

FORM PTO-1390 (REV. 9-2001)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER PHA 4159.26	
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/009447	
INTERNATIONAL APPLICATION NO. PCT/US00/09806		INTERNATIONAL FILING DATE 17 May 2000		PRIORITY DATE CLAIMED 19 May 1999	
TITLE OF INVENTION SUBSTITUTED POLYCYCLIC ARYL AND HETEROARYL PYRIMIDINONES USEFUL AS ANTICOAGULANTS					
APPLICANT(S) FOR DO/EO/US MONSANTO COMPANY					
<p>Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:</p> <ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ol style="list-style-type: none"> a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> has been communicated by the International Bureau c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). <ol style="list-style-type: none"> a. <input type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)). <ol style="list-style-type: none"> a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made, however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). <p>Items 11 to 20 below concern document(s) or information included:</p> <ol style="list-style-type: none"> 11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. 14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A change of power of attorney and/or address letter. 17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1 821-1 825. 18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4) 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 20. <input type="checkbox"/> Other items or information: 					

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 10/009447		INTERNATIONAL APPLICATION NO. PCT/US00/09806		ATTORNEY'S DOCKET NUMBER PHA 4159.26	
21. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00 International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00 International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS PTO USE ONLY	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e))				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	481- 20 =	461	x \$18.00	\$ 8298 00	
Independent claims	2- 3 =		x \$84.00	\$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$280.00	\$ 280.00	
TOTAL OF ABOVE CALCULATIONS =				\$ 9468.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2				\$	
SUBTOTAL =				\$	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
TOTAL NATIONAL FEE =				\$ 9468.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$	
TOTAL FEES ENCLOSED =				\$ 9468.00	
				Amount to be refunded:	\$
				charged:	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ 9468 00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-1345. A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: Kathryn J. Doty Senniger, Powers, Leavitt & Roedel One Metropolitan Square, 16th Floor St. Louis, Missouri 63102					
				SIGNATURE <u>Kathryn J. Doty</u> NAME Kathryn J. Doty REGISTRATION NUMBER 40,593	

PHA 4159.26
Patents

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of M. South et al. Art Unit TBA
Serial No. TBA
Filed TBA
Confirmation No. TBA
For SUBSTITUTED POLYCYCLIC ARYL AND HETEROARYL PYRYMIDINONES
USEFUL FOR ANTICOAGULANTS
Examiner TBA

November 13, 2001

PRELIMINARY AMENDMENT A

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS,

SIR:

Please enter the following amendments before examination of
the above referenced application:

IN THE CLAIMS

Substitute the following for claim 38:

38. (once amended) A composition for inhibiting thrombotic
conditions in blood comprising a compound of any one of Claims 8,
16, 24, 32, or 37 and a pharmaceutically acceptable carrier.

Substitute the following for claim 39:

39. (once amended) A composition for inhibiting thrombotic
conditions in blood comprising a compound of any one of Claims 1
through 7, Claims 9 through 15, Claims 17 through 23, Claims 25
through 31, or Claims 33 through 36 and a pharmaceutically
acceptable carrier.

PHA 4159.26
Patents

Substitute the following for claim 40:

40. (once amended) A method for inhibiting thrombotic conditions in blood comprising adding to blood a therapeutically effective amount of a composition of any one of Claims 1 through 37.

Substitute the following for claim 41:

41. (once amended) A method for inhibiting formation of blood platelet aggregates in blood comprising adding to blood a therapeutically effective amount of a composition of any one of Claims 1 through 37.

Substitute the following for claim 42:

42. (once amended) A method for inhibiting thrombus formation in blood comprising adding to blood a therapeutically effective amount of a composition of any one of Claims 1 through 37.

Substitute the following for claim 43:

43. (once amended) A method for treating or preventing venous thromboembolism and pulmonary embolism in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 1 through 37.

Substitute the following for claim 44:

44. (once amended) A method for treating or preventing deep vein thrombosis in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 1 through 37.

PHA 4159.26
Patents

Substitute the following for claim 45:

45. (once amended) A method for treating or preventing cardiogenic thromboembolism in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 1 through 37.

Substitute the following for claim 46:

46. (once amended) A method for treating or preventing thromboembolic stroke in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 1 through 37.

Substitute the following for claim 47:

47. (once amended) A method for treating or preventing thrombosis associated with cancer and cancer chemotherapy in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 1 through 37.

Substitute the following for claim 48:

48. (once amended) A method for treating or preventing unstable angina in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 1 through 37.

PHA 4159.26
Patents

REMARKS

Applicants have elected to amend the original claims solely for the purpose of prosecuting the amended claims in this application. These amended claims better encompass the full breadth of certain aspects of the present invention, notwithstanding applicants' belief that the original claims directed toward these aspects would have been allowable.

Favorable consideration and early allowance of all pending claims is requested.

PHA 4159.26
Patents

VERSION WITH MARKINGS TO SHOW CHANGES MADE

CLAIM 38:

38. (once amended) A composition for inhibiting thrombotic conditions in blood comprising a compound of any one of Claims 8, 16, 24, 32, [and] or 37 and a pharmaceutically acceptable carrier.

CLAIM 39:

39. (once amended) A composition for inhibiting thrombotic conditions in blood comprising a compound of any one of Claims 1 through 7, Claims 9 through 15, Claims 17 through 23, Claims 25 through 31, [and] or Claims 33 through 36 and a pharmaceutically acceptable carrier.

CLAIM 40:

40. (once amended) A method for inhibiting thrombotic conditions in blood comprising adding to blood a therapeutically effective amount of a composition of any one of Claims [38 and 39] 1 through 37.

CLAIM 41:

41. (once amended) A method for inhibiting formation of blood platelet aggregates in blood comprising adding to blood a therapeutically effective amount of a composition of any one of Claims [38 and 39] 1 through 37.

CLAIM 42:

42. (once amended) A method for inhibiting thrombus formation in blood comprising adding to blood a therapeutically

PHA 4159.26
Patents

effective amount of a composition of any one of Claims [38 and 39] 1 through 37.

CLAIM 43:

43. (once amended) A method for treating or preventing venous thromboembolism and pulmonary embolism in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims [38 and 39] 1 through 37.

CLAIM 44:

44. (once amended) A method for treating or preventing deep vein thrombosis in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims [38 and 39] 1 through 37.

CLAIM 45:

45. (once amended) A method for treating or preventing cardiogenic thromboembolism in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims [38 and 39] 1 through 37.

CLAIM 46:

46. (once amended) A method for treating or preventing thromboembolic stroke in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims [38 and 39] 1 through 37.

PHA 4159.26
Patents

CLAIM 47:

47. (once amended) A method for treating or preventing thrombosis associated with cancer and cancer chemotherapy in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims [38 and 39] 1 through 37.

CLAIM 48:

48. (once amended) A method for treating or preventing unstable angina in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims [38 and 39] 1 through 37.

310019447 040302

PHA 4159.26
Patents

The Commissioner is hereby authorized to charge any
deficiency or overpayment of the required fee to Deposit Account
No. 19-1345.

Respectfully submitted,



Kathryn J. Doty, Reg. No. 40,593
SENNIGER, POWERS, LEAVITT & ROEDEL
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

Express Mail Label No. EL 739388090 US

JC07 Rec'd PCT/PTO 13 NOV 2001
10/009447

Field of the Invention

Background of the Invention

Plasma coagulation factors include factors II, V, VII, VIII, IX, X, XI, and XII; these are also called protease zymogens. These coagulation factors or protease zymogens are activated by serine proteases leading to coagulation in a so called “coagulation cascade” or chain reaction [Handin, R. I.: Bleeding and Thrombosis. In Wilson, J., et al. editors: Harrison’s Principles of Internal Medicine. 12th Edition, New York, McGraw-Hill Book Co., 1991,p.350].

Coagulation or clotting occurs in two ways through different pathways. An intrinsic or contact pathway leads from XII to XIIa to XIa to IXa and to the conversion of X to Xa. Xa with factor Va converts prothrombin (II) to thrombin (IIa) leading to conversion of fibrinogen to fibrin. Polymerization of fibrin leads to a fibrin clot. An extrinsic pathway is initiated by the conversion of coagulation factor VII to VIIa by Xa. The presence of Tissue Factor and

VIIa accelerates formation of Xa in the presence of calcium ion and phospholipids. Formation of Xa leads to thrombin, fibrin, and a fibrin clot as described above. The presence of one or more of these many different coagulation factors and two distinct pathways of clotting could enable the
 5 efficacious, selective control and better understanding of parts of the coagulation or clotting process.

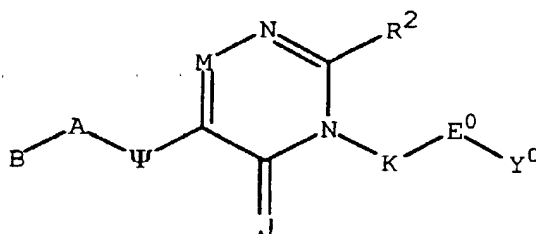
While clotting as a result of an injury to a blood vessel is a critical physiological process for mammals such as man, clotting can also lead to disease states. A pathological process called thrombosis results when platelet
 10 aggregation and/or a fibrin clot blocks (i.e., occludes) a blood vessel. Arterial thrombosis may result in ischemic necrosis of the tissue supplied by the artery. When the thrombosis occurs in a coronary artery, a myocardial infarction or heart attack can result. A thrombosis occurring in a vein may cause tissues drained by the vein to become edematous and inflamed. Thrombosis of a deep
 15 vein may be complicated by a pulmonary embolism. Preventing or treating clots in a blood vessel may be therapeutically useful by inhibiting formation of blood platelet aggregates, inhibiting formation of fibrin, inhibiting thrombus formation, inhibiting embolus formation, and for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic
 20 attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels.

There have been several reports of non-peptidic and peptidic pyrimidinone compounds that act as an inhibitor of a coagulation factor present
 25 in the coagulation cascade or clotting process. In PCT Patent Application WO 98/47876, Van Boeckel et al. describe peptidic 6-alkylpyridones and 2-alkylpyrimidinones as anti-thrombotic compounds. In PCT Patent Application WO 98/16547, Zhu and Scarborough describe 3-(N-heterocycllamino)-4,5,6-substituted-pyridonylacetamides and 2,4-substituted-5-(N-heterocycllamino)-
 30 pyrimidinonyl-acetamides containing amide substituents and having activity against mammalian factor Xa. In US Patent 5,656,645, Tamura et al. describe 4,5,6-substituted-3-aminopyridonyl-acetamides, 1,6-substituted-5-aminouracinylnacetamides, and 2,4-substituted-5-aminopyrimidinonyl-acetamides containing amide substituents having a formyl function and having
 35 activity against thrombin. In US Patent 5,658,930, Tamura et al. again

- describe 4,5,6-substituted-3-aminopyridonyl-acetamides, 1,6-substituted-5-aminouracinylnacetamides, and 2,4-substituted-5-aminopyrimidinonyl-acetamides containing amide substituents having a formyl function and having activity against thrombin. In PCT Patent Applications 96/18644 and 97/46207,
- 5 Tamura et al. further describe 4,5,6-substituted-3-aminopyridonylnacetamides, 1,6-substituted-5-aminouracinylnacetamides, and 2,4-substituted-5-aminopyrimidinonylnacetamides containing amide substituents having a formyl function and having activity against thrombin. In PCT Patent Application WO 98/09949, Suzuki et al. describe 2-heterocyclyacetamido derivatives of 1,2-diketones and report that they inhibit proteases, especially chymase inhibitors.
- 10

SUMMARY OF THE INVENTION

- 15 It is an object of the present invention to provide compounds that are beneficial in anticoagulant therapy and that have a general structure:



Formula (I).

- 20 It is another object of the present invention to provide methods for preventing and treating thrombotic conditions, such as coronary artery disease, cerebrovascular disease, and other coagulation related disorders. Such thrombotic conditions are prevented and treated by administering to a patient in need thereof an effective amount of compounds of Formula (I).

- 25 Various other objects and advantages of the present invention will become apparent from the following description of the invention.

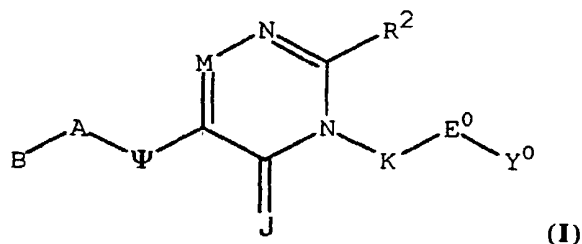
DESCRIPTION OF THE INVENTION

The present invention relates to a class of compounds comprising Substituted Polycyclic Aryl and Heteroaryl pyrimidinones, which are beneficial in anticoagulant therapy for the treatment and prevention of a variety of

WO 00/69832

PCT/US00/09806

thrombotic conditions including coronary artery and cerebrovascular disease,
as given in Formula (I):



or a pharmaceutically acceptable salt thereof, wherein;

5 J is selected from the group consisting of O and S;

J is optionally selected from the group consisting of CH-R^6 and N-R^6

wherein R^6 is a linear spacer moiety having a chain length of 1 to 4 atoms

linked to the point of bonding of a substituent selected from the group

consisting of R^{4a} , R^{4b} , R^{39} , R^{40} , R^5 , R^{14} , and R^{15} to form a heterocyclyl

10 ring having 5 through 8 contiguous members;

J is optionally selected from the group consisting of CH-R^6 and N-R^6

wherein R^6 is a linear spacer moiety having a chain length of 1 to 4 atoms

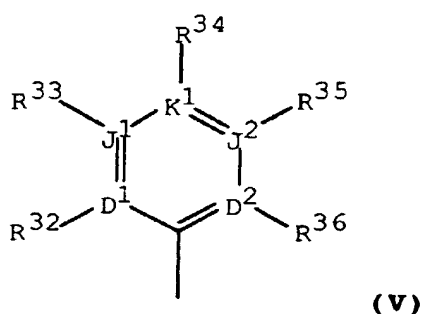
linked to the points of bonding of both R^{4a} and R^{4b} to form a heterocyclyl ring
having 5 through 8 contiguous members;

15 J is optionally selected from the group consisting of CH-R^6 and N-R^6

wherein R^6 is a linear spacer moiety having a chain length of 1 to 4 atoms

linked to the points of bonding of both R^{39} and R^{40} to form a heterocyclyl
ring having 5 through 8 contiguous members;

B is formula (V):



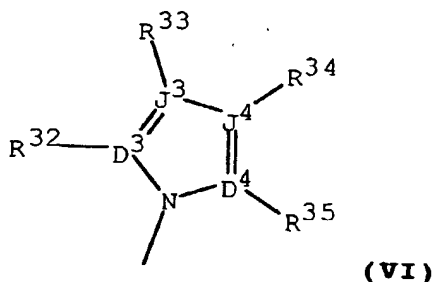
- wherein D^1 , D^2 , J^1 , J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one can be a covalent bond, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is O, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is S, one of D^1 , D^2 , J^1 , J^2 and K^1 must be a covalent bond when two of D^1 , D^2 , J^1 , J^2 and K^1 are O and S, and no more than four of D^1 , D^2 , J^1 , J^2 and K^1 are N with the proviso that R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{16} , R^{17} , R^{18} , R^{19} , R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aryloylalkoxy, heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroaryl amino, N-heteroaryl amino-N-alkyl amino, heteroaryl aminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy,

- halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, alkoxyamino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, 5 arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, 10 arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclisulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower 15 cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, alkylenylamino, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, 20 carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboxy, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl;
- 25 R^{16} , R^{19} , R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;
- R^{32} and R^{33} , R^{33} and R^{34} , R^{34} and R^{35} , and R^{35} and R^{36} are 30 independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through

8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the proviso that no more than one of the group consisting of spacer pairs R^{32} and R^{33} , R^{33} and R^{34} , R^{34} and R^{35} , and R^{35} and R^{36} are used at the same time;

- 5 R^9 and R^{10} , R^{10} and R^{11} , R^{11} and R^{12} , and R^{12} and R^{13} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through
- 10 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the proviso that no more than one of the group consisting of spacer pairs R^9 and R^{10} , R^{10} and R^{11} , R^{11} and R^{12} , and R^{12} and R^{13} are used at the same time;

- 15 B is optionally formula (VI):



- wherein D^3 , D^4 , J^3 , and J^4 are independently selected from the group consisting of C, N, O, and S, no more than one of D^3 , D^4 , J^3 , and J^4 is O, no more than one of D^3 , D^4 , J^3 , and J^4 is S, and no more than three of D^1 , D^2 , J^1 , and J^2 are N with the proviso that R^{32} , R^{33} , R^{34} , and R^{35} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- 20

B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2-C8 alkyl, C3-C8 alkenyl, C3-C8 alkylenyl, C3-C8 alkynyl, C2-C8 haloalkyl, and C3-C8 haloalkenyl wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R³², R³³,

R³⁴, R³⁵, and R³⁶;

B is optionally selected from the group consisting of C3-C15 cycloalkyl, C5-C10 cycloalkenyl, C4-C12 saturated heterocyclyl, and C4-C9 partially saturated heterocyclyl, wherein each ring carbon is optionally

substituted with R³³, a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R⁹ or R¹³, a ring carbon or nitrogen atom adjacent to the R⁹ position and two atoms from the point of attachment is optionally substituted with R¹⁰, a ring carbon or nitrogen atom adjacent to the R¹³ position and two atoms from the point of attachment is optionally substituted with R¹², a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R¹⁰ position is optionally substituted with R¹¹, a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R¹² position is optionally substituted with R³³, and a ring carbon or nitrogen atom four atoms from the point of attachment and adjacent to the R¹¹ and R³³ positions is optionally substituted with R³⁴;

A is selected from the group consisting of single covalent bond, (W⁷)_{rr}-(CH(R¹⁵))_{pa} and (CH(R¹⁵))_{pa}-(W⁷)_{rr} wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 6, and W⁷ is selected from the group consisting of O, S, C(O), C(S), C(O)S, C(S)O,

$C(O)N(R^7)$, $C(S)N(R^7)$, $(R^7)NC(O)$, $(R^7)NC(S)$, $S(O)$, $S(O)_2$,
 $S(O)_2N(R^7)$, $(R^7)NS(O)_2$, $Se(O)$, $Se(O)_2$, $Se(O)_2N(R^7)$, $(R^7)NSe(O)_2$,
 $P(O)(R^8)$, $N(R^7)P(O)(R^8)$, $P(O)(R^8)N(R^7)$, $C(NR^7)N(R^7)$, $(R^7)NC(NR^7)$,
 $(R^7)NC(NR^7)NR^7$, and $N(R^7)$ with the proviso that no more than one of the

5 group consisting of rr and pa is 0 at the same time;

R^7 and R^8 are independently selected from the group consisting of
hydrido, hydroxy, alkyl, alkenyl, aryl, aralkyl, aryloxy, alkoxy, alkenyloxy,
alkylthio, alkylamino, arylthio, arylamino, acyl, aroyl, heteroaroyl,
aralkoxyalkyl, heteroaralkoxyalkyl, , aryloxyalkyl, alkoxyalkyl,
10 alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, aralkoxyalkyl,
heteroaralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, heteroaryl,
heteroaryloxy, heteroarylamino, heteroaralkyl, heteroaralkyloxy,
heteroaralkylamino, and heteroaryloxyalkyl;

R^{14} , R^{15} , R^{37} , R^{38} , R^{39} , R^{40} , R^{41} and R^{42} are independently
15 selected from the group consisting of amidino, hydroxyamino, hydrido,
hydroxy, halo, cyano, aryloxy, amino, alkylamino, dialkylamino,
hydroxyalkyl, aminoalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl,
sulfhydryl, acylamido, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl,
aryl, aralkyl, aryloxyalkyl, aralkoxyalkylalkoxy, alkylsulfinylalkyl,
20 alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl,
heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl,
cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl,
haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy, haloalkoxyalkyl,
haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl,
25 halocycloalkenyloxyalkyl, saturated heterocyclyl, partially saturated
heterocyclyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl,
heteroaralkylthioalkyl, monocarboalkoxyalkyl, dicarboalkoxyalkyl,
monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, alkylsulfinyl,
alkylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, arylsulfinyl,
30 arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, aralkylsulfinyl,
aralkylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, cycloalkylsulfinylalkyl,

- cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, carboxamidoalkyl, carboaralkoxy, trialkylsilyl, dialkoxyposphono, 5 diaralkoxyposphono, dialkoxyposphonoalkyl, and diaralkoxyposphonoalkyl with the proviso that R^{37} and R^{38} are independently selected from other than formyl and 2-oxoacyl; R^{14} and R^{14} , when bonded to different carbons, are optionally taken together to form a group selected from the group consisting of covalent bond, 10 alkylene, haloalkylene, and a linear moiety spacer selected to form a ring selected from the group consisting of cycloalkyl ring having from 5 through 8 contiguous members, cycloalkenyl ring having from 5 through 8 contiguous members, and a heterocyclyl having from 5 through 8 contiguous members; R^{14} and R^{15} , when bonded to different carbons, are optionally taken 15 together to form a group selected from the group consisting of covalent bond, alkylene, haloalkylene, and a linear moiety spacer selected to form a ring selected from the group consisting of a cycloalkyl ring having from 5 through 8 contiguous members, a cycloalkenyl ring having from 5 through 8 contiguous members, and a heterocyclyl having from 5 through 8 contiguous members; 20 R^{15} and R^{15} , when bonded to different carbons, are optionally taken together to form a group selected from the group consisting of covalent bond, alkylene, haloalkylene, and a linear moiety spacer selected to form a ring selected from the group consisting of cycloalkyl ring having from 5 through 8 contiguous members, cycloalkenyl ring having from 5 through 8 contiguous 25 members, and a heterocyclyl having from 5 through 8 contiguous members; Ψ is selected from the group consisting of NR^5 , O, C(O), C(S), S, S(O), S(O)₂, ON(R^5), P(O)(R^8), and CR³⁹R⁴⁰; R^5 is selected from the group consisting of hydrido, hydroxy, amino, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxy, aralkoxy, alkoxy, alkenyloxy, 30 alkylthio, arylthio, aralkoxyalkyl, heteroaralkoxyalkyl, aryloxyalkyl, alkoxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, aralkoxyalkyl,

heteroaralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, heteroaryl, heteroarylalkyl, monocarboalkoxyalkyl, monocarboalkoxy, dicarboalkoxyalkyl, monocarboxamido, monocyanoalkyl, dicyanoalkyl, carboalkoxycyanoalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, and dialkoxyphosphonoalkyl;

5

R^{39} and R^{40} , when bonded to the same carbon, are optionally taken

- 10 together to form a group selected from a group consisting of oxo, thiono, R^5 -N, alkylene, haloalkylene, and a linear moiety spacer having from 2 through 7 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8 contiguous members, and a heterocyclyl ring
- 15 having from 3 through 8 contiguous members;

M is selected from the group consisting of N and R^1 -C;

R^2 and R^1 are independently selected from the group consisting of Z^0 -Q, hydrido, alkyl, alkenyl, and halo;

- 20 R^1 is optionally selected from the group consisting of amino, aminoalkyl, alkylamino, amidino, guanidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, alkylthio, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, heteroarylamine, nitro, arylamine, aralkylamine, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, hydroxyhaloalkyl, cyano, and phosphono;

- 25 R^2 is optionally selected from the group consisting of amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, heteroarylamine, amino, nitro, alkylamine, arylamine, aralkylamine, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, hydroxyhaloalkyl, cyano, and phosphono;

- 30 R^2 and R^{4a} , R^2 and R^{4b} , R^2 and R^{14} , and R^2 and R^{15} are optionally independently selected to form spacer pairs wherein a spacer pair is taken together to form a linear moiety having from 2 through 5 contiguous atoms

connecting the points of bonding of said spacer pair members to form a heterocyclyl ring having from 5 through 8 contiguous members with the proviso that no more than one of the group of spacer pairs consisting of R^2 and R^{4a} , R^2 and R^{4b} , R^2 and R^{14} , and R^2 and R^{15} is used at the same time;

- 5 R^2 is optionally independently selected to form a linear moiety having from 2 through 5 contiguous atoms linked to the points of bonding of both R^{4a} and R^{4b} to form a heterocyclyl ring having from 5 through 8 contiguous members;

Z^0 is selected from the group consisting of covalent single bond,

- 10 $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 6, $(CH(R^{41}))_g$ - W^0 -($CH(R^{42}))_p$ wherein g and p are integers independently selected from 0 through 3 and W^0 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{41}), (R^{41})NC(O), C(S)N(R^{41}), (R^{41})NC(S), OC(O)N(R^{41}), (R^{41})NC(O)O, SC(S)N(R^{41}), (R^{41})NC(S)S, SC(O)N(R^{41}), (R^{41})NC(O)S, OC(S)N(R^{41}), (R^{41})NC(S)O, N(R^{42})C(O)N(R^{41}), (R^{41})NC(O)N(R^{42}), N(R^{42})C(S)N(R^{41}), (R^{41})NC(S)N(R^{42}), S(O), S(O)₂, S(O)₂N(R^{41}), N(R^{41})S(O)₂, Se, Se(O), Se(O)₂, Se(O)₂N(R^{41}), N(R^{41})Se(O)₂, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^{41}), ON(R^{41}), and SiR²⁸R²⁹, and $(CH(R^{41}))_e$ - W^{22} -
 15 $(CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^{22} is selected from the group consisting of $CR^{41}=CR^{42}$, $CR^{41}R^{42}=C$; vinylidene), ethynylidene ($C\equiv C$; 1,2-ethynyl), 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-

morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the provisos that R⁴¹ and R⁴² are selected from other than halo and cyano when directly bonded to N and Z⁰ is directly bonded to the pyrimidinone ring:

R²⁸ and R²⁹ are independently selected from the group consisting of

10 hydrido, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl,

15 haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl,

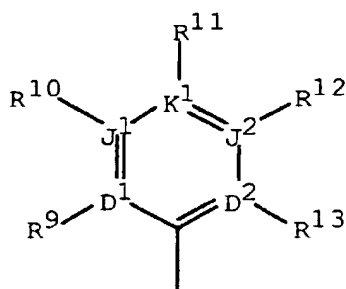
20 carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, aralkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl,

25 aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, dialkoxyposphono, diaralkoxyposphono, dialkoxyposphonoalkyl and diaralkoxyposphonoalkyl;

R²⁸ and R²⁹ are optionally taken together to form a linear moiety spacer having from 2 through 7 contiguous atoms and forming a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous

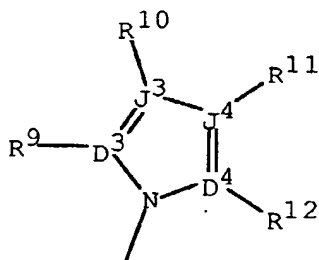
30 members, a cycloalkenyl ring having from 3 through 8 contiguous members, and a heterocyclyl ring having from 3 through 8 contiguous members;

Q is formula (II):



(II)

- wherein D¹, D², J¹, J² and K¹ are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one can be a covalent bond, no more than one of D¹, D², J¹, J² and K¹ can be O, no more than one of D¹, D², J¹, J² and K¹ can be S, one of D¹, D², J¹, J² and K¹ must be a covalent bond when two of D¹, D², J¹, J² and K¹ are O and S, and no more than four of D¹, D², J¹, J² and K¹ can be N, with the proviso that R⁹, R¹⁰, R¹¹, R¹², and R¹³ are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- Q is optionally selected from formula (III):



(III)

- wherein D³, D⁴, J³, and J⁴ are independently selected from the group consisting of C, N, O, and S, no more than one of D³, D⁴, J³, and J⁴ is O, no more than one of D³, D⁴, J³, and J⁴ is S, and no more than three of D¹, D²,

J^1 , and J^2 are N with the proviso that R^9 , R^{10} , R^{11} , and R^{12} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

- 5 Q is optionally selected from the group consisting of hydrido, alkyl, alkoxy, alkylamino, alkylthio, haloalkylthio, alkenyl, alkynyl, saturated heterocyclyl, partially saturated heterocyclyl, acyl, aroyl, heteroaroyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkylalkenyl, haloalkyl, haloalkoxy, haloalkenyl, halocycloalkyl, halocycloalkenyl, 10 haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, and halocycloalkenyloxyalkyl with the proviso that Z^0 is selected from other than a single covalent bond when Q is hydrido;

K is $(CR^{4a}R^{4b})_n$ wherein n is an integer selected from 1 through 4;

- R^{4a} and R^{4b} are independently selected from the group consisting of 15 halo, hydrido, hydroxy, cyano, hydroxyalkyl, alkyl, alkenyl, aryl, aralkyl, aralkoxyalkyl, aryloxyalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, aralkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, haloalkenyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl, alkylsulfinylalkyl, 20 alkylsulfonylalkyl, haloalkylsulfinyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, and aralkylsulfonylalkyl with the provisos that halo, hydroxy, and cyano are bonded to different carbons when simultaneously present and that R^{4a} and R^{4b} 25 are other than hydroxy or cyano when bonded to the carbon directly bonded to the pyrimidinone nitrogen;

- R^{4a} and R^{4b} , when bonded to the same carbon, are optionally taken together to form a group selected from the group consisting of oxo, thiono, and a linear spacer moiety having from 2 through 7 contiguous atoms connected to form a ring selected from the group consisting of a cycloalkyl ring having 3 30 through 8 contiguous members, a cycloalkenyl ring having 5 through 8 contiguous members, and a heterocyclyl ring having 5 through 8 contiguous

members with the proviso that R^{4a} and R^{4b} taken together is other than oxo or thiono when the common carbon is directly bonded to the pyrimidinone nitrogen;

- E^0 is E^1 , when K is $(CR^{4a}R^{4b})_n$, wherein E^1 is selected from the
- 5 group consisting of a covalent single bond, O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^7), (R^7)NC(O), C(S)N(R^7), (R^7)NC(S), OC(O)N(R^7), (R^7)NC(O)O, SC(S)N(R^7), (R^7)NC(S)S, SC(O)N(R^7), (R^7)NC(O)S, OC(S)N(R^7), (R^7)NC(S)O, N(R^8)C(O)N(R^7), (R^7)NC(O)N(R^8), N(R^8)C(S)N(R^7), (R^7)NC(S)N(R^8), S(O), S(O)₂, S(O)₂N(R^7), N(R^7)S(O)₂, S(O)₂N(R^7)C(O), C(O)N(R^7)S(O)₂, Se, Se(O), Se(O)₂, Se(O)₂N(R^7), N(R^7)Se(O)₂, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^7), ON(R^7), SiR²⁸R²⁹, CR^{4a}=CR^{4b}, ethynylidene (C≡C; 1,2-ethynyl), and C=CR^{4a}R^{4b};
- 10

- K is optionally selected to be $(CH(R^{14}))_j-T$ wherein j is selected from a
- 15 integer from 0 through 3 and T is selected from the group consisting of single covalent bond, O, S, and N(R^7) with the provisos that R^{14} is other than hydroxy, cyano, halo, amino, alkylamino, dialkylamino, and sulfhydryl when j is 1 and that $(CH(R^{14}))_j$ is bonded to the pyrimidinone ring;

- E^0 is optionally E^2 , when K is $(CH(R^{14}))_j-T$, wherein E^2 is selected
- 20 from the group consisting of a covalent single bond, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^7), (R^7)NC(O), C(S)N(R^7), (R^7)NC(S), (R^7)NC(O)O, (R^7)NC(S)S, (R^7)NC(O)S, (R^7)NC(S)O, N(R^8)C(O)N(R^7), (R^7)NC(O)N(R^8), N(R^8)C(S)N(R^7), (R^7)NC(S)N(R^8), S(O), S(O)₂,

- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is independently selected from the group consisting of C and N^+ , no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more
- 5 than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, no more than three of D^5 , D^6 , J^5 , and J^6 are N when K^2 is N^+ , and no more than four of D^5 , D^6 , J^5 , and J^6 are N when K^2 is carbon with the provisos that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature
- 10 of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- R^{16} and R^{17} are independently optionally taken together to form a linear moiety spacer having from 3 through 6 contiguous atoms connected to form a ring selected from the group consisting of a cycloalkenyl ring having
- 15 from 5 through 8 contiguous members, a partially saturated heterocyclyl ring having from 5 through 8 contiguous members, a heteroaryl having from 5 through 6 contiguous members, and an aryl;
- R^{18} and R^{19} are independently optionally taken together to form a linear moiety spacer having from 3 through 6 contiguous atoms connected to
- 20 form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members, a partially saturated heterocyclyl ring having from 5 through 8 contiguous members, a heteroaryl having from 5 through 6 contiguous members, and an aryl;
- Q^b is selected from the group consisting of $NR^{20}R^{21}$,
- 25 $+NR^{20}R^{21}R^{22}$, oxy, alkyl, aminoalkylenyl, alkylamino, dialkylamino, dialkylsulfoniumalkyl, acylamino and Q^{be} wherein Q^{be} is hydrido and R^{20} ,

$C(O)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $C(S)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$,
 $N(R^{26})N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $ON(R^{26})C(NR^{25})N(R^{23})(R^{24})$,
 $N(R^{26})N(R^{26})SO_2N(R^{23})(R^{24})$, $C(NR^{25})SR^5$, $C(O)NR^{23}R^{24}$, and
 $C(O)NR^{23}R^{24}$ with the provisos that no more than one of R^{23} , R^{24} , and R^{26}

- 5 can be hydroxy, alkoxy, alkylamino, amino, or dialkylamino when any two of the group consisting of R^{23} , R^{24} , and R^{26} are bonded to the same atom and that said Q^b group is bonded directly to a carbon atom;

- R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, alkoxy, alkylenylamino, amino,
 10 alkylamino, dialkylamino, and hydroxyalkyl;

R^{23} and R^{24} are optionally taken together to form a linear spacer moiety having from 4 through 7 contiguous atoms connecting the points of bonding to form a heterocyclyl ring having 5 through 8 contiguous members;

- R^{23} and R^{25} , R^{24} and R^{25} , R^{25} and R^{26} , R^{24} and R^{26} , and R^{23} and
 15 R^{26} are independently optionally selected to form a spacer pair wherein a spacer pair is taken together from the points of bonding of selected spacer pair members to form the group L-U-V wherein L, U, and V are independently selected from the group consisting of O, S, C(O), C(S), C(J_H)₂, S(O), SO₂, OP(OR³¹)R³⁰,
 $P(O)R^{30}$, $P(S)R^{30}$, $C(R^{30})R^{31}$, $C=C(R^{30})R^{31}$, $(O)_2POP(O)_2$,
 20 $R^{30}(O)POP(O)R^{30}$, $Si(R^{29})R^{28}$, $Si(R^{29})R^{28}Si(R^{29})R^{28}$,
 $Si(R^{29})R^{28}OSi(R^{29})R^{28}$, $(R^{28})R^{29}COC(R^{28})R^{29}$, $(R^{28})R^{29}CSC(R^{28})R^{29}$,
 $C(O)C(R^{30})=C(R^{31})$, $C(S)C(R^{30})=C(R^{31})$, $S(O)C(R^{30})=C(R^{31})$,
 $SO_2C(R^{30})=C(R^{31})$, $PR^{30}C(R^{30})=C(R^{31})$, $P(O)R^{30}C(R^{30})=C(R^{31})$,
 $P(S)R^{30}C(R^{30})=C(R^{31})$, $DC(R^{30})(R^{31})D$, $OP(OR^{31})R^{30}$, $P(O)R^{30}$, $P(S)R^{30}$,

$\text{Si}(\text{R}^{28})\text{R}^{29}$ and $\text{N}(\text{R}^{30})$, and a covalent bond with the proviso that no more than any two of L, U and V are simultaneously covalent bonds and the heterocyclyl comprised of by L, U, and V has from 5 through 10 contiguous member;

D is selected from the group consisting of oxygen, C=O, C=S, $\text{S}(\text{O})_m$

5 wherein m is an integer selected from 0 through 2;

J_H is independently selected from the group consisting of OR^{27} , SR^{27} and $\text{N}(\text{R}^{20})\text{R}^{21}$;

R^{27} is selected from the group consisting of hydrido, alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl and aralkylsulfonylalkyl;

R^{30} and R^{31} are independently selected from the group consisting of hydrido, hydroxy, thiol, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyposphonoalkyl, diaralkoxyposphonoalkyl, phosphonoalkyl, dialkoxyposphonoalkoxy, diaralkoxyposphonoalkoxy, phosphonoalkoxy, dialkoxyposphonoalkylamino,

diaralkoxyphosphonoalkylamino, phosphonoalkylamino,
 dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl,
 alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy,
 aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxysulfonylalkylamino,
 5 aralkoxysulfonylalkylamino, and sulfonylalkylamino;

R^{30} and R^{31} are optionally taken to form a linear moiety spacer group
 having from 2 through 7 contiguous atoms to form a ring selected from the group
 consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a
 cycloalkenyl ring having from 3 through 8 contiguous members, and a
 10 heterocyclyl ring having from 3 through 8 contiguous members;
 R^{23} and R^{25} , R^{24} and R^{25} , R^{25} and R^{26} , R^{24} and R^{26} , and R^{23} and
 R^{26} are independently optionally selected to form a spacer pair wherein a spacer
 pair is taken together from the points of bonding of selected spacer pair members to
 form the group L-U-V wherein L, U, and V are independently selected from the
 15 group of 1,2-disubstituted radicals consisting of a cycloalkyl radical, a cycloalkenyl
 radical wherein cycloalkyl and cycloalkenyl radicals are substituted with one or
 more groups selected from R^{30} and R^{31} , an aryl radical, an heteroaryl radical, a
 saturated heterocyclic radical and a partially saturated heterocyclic radical wherein
 said 1,2-substitutents are independently selected from C=O, C=S, $C(R^{28})R^{32}$,
 20 S(O), S(O)₂, OP(OR³¹)R³⁰, P(O)R³⁰, P(S)R³⁰ and Si(R²⁸)R²⁹;
 R^{23} and R^{25} , R^{24} and R^{25} , R^{25} and R^{26} , R^{24} and R^{26} , and R^{23} and
 R^{26} are independently optionally selected to form a spacer pair wherein a spacer
 pair is taken together from the points of bonding of selected spacer pair members to
 form the group L-U-V wherein L, U, and V are independently selected from the
 25 group of radicals consisting of 1,2-disubstituted alkylene radicals and 1,2-
 disubstituted alkenylene radical wherein said 1,2-substitutents are independently
 selected from C=O, C=S, $C(R^{28})R^{29}$, S(O), S(O)₂, OP(OR³¹)R³⁰, P(O)R³⁰,

$P(S)R^{30}$, and $Si(R^{28})R^{29}$ and said alkylene and alkenylene radical are substituted with one or more R^{30} or R^{31} substituents;

Q^S is selected from the group consisting of a single covalent bond.

$(CR^{37}R^{38})_b-(W^0)_{az}$ wherein az is an integer selected from 0 through 1, b is

5 an integer selected from 1 through 4, and W^0 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{14}), (R^{14})NC(O), C(S)N(R^{14}), (R^{14})NC(S), OC(O)N(R^{14}), SC(S)N(R^{14}), SC(O)N(R^{14}), OC(S)N(R^{14}), N(R^{15})C(O)N(R^{14}), (R^{14})NC(O)N(R^{15}), N(R^{15})C(S)N(R^{14}), (R^{14})NC(S)N(R^{15}), S(O), S(O)₂, S(O)₂N(R^{14}),

10 N(R^{14})S(O)₂, Se, Se(O), Se(O)₂, Se(O)₂N(R^{17}), N(R^{14})Se(O)₂, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^{14}), ON(R^{14}), and $SiR^{28}R^{29}$,

$(CH(R^{14}))_c-W^1-(CH(R^{15}))_d$ wherein c and d are integers independently

selected from 1 through 4, and W^1 is selected from the group consisting of O,

S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{14}), (R^{14})NC(O),

15 C(S)N(R^{14}), (R^{14})NC(S), OC(O)N(R^{14}), (R^{14})NC(O)O, SC(S)N(R^{14}), (R^{14})NC(S)S, SC(O)N(R^{14}), (R^{14})NC(O)S, OC(S)N(R^{14}), (R^{14})NC(S)O, N(R^{15})C(O)N(R^{14}), (R^{14})NC(O)N(R^{15}), N(R^{15})C(S)N(R^{14}),

(R^{14})NC(S)N(R^{15}), S(O), S(O)₂, S(O)₂N(R^{14}), N(R^{14})S(O)₂, Se, Se(O),

Se(O)₂, Se(O)₂N(R^{14}), N(R^{14})Se(O)₂, P(O)(R^8), N(R^7)P(O)(R^8),

20 P(O)(R^8)N(R^7), N(R^{14}), ON(R^{14}), $SiR^{28}R^{29}$, and $(CH(R^{14}))_e-W^{22}-$

$(CH(R^{15}))_h$ wherein e and h are integers independently selected from 0

- through 2 and W²² is selected from the group consisting of CR⁴¹=CR⁴²,
 CR⁴¹R⁴²=C; vinylidene), ethynylidene (C≡C; 1,2-ethynyl), 1,2-cyclopropyl,
 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-
 cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-
 5 morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-
 piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl,
 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-
 pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-
 pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-
 10 tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the provisos that R¹⁴ and
 R¹⁵ are selected from other than halo and cyano when directly bonded to N
 and that (CR³⁷R³⁸)_b, (CH(R¹⁴))_c, (CH(R¹⁴))_e and are bonded to E⁰;
 R³⁷ and R³⁸, when bonded to different carbons, are optionally taken
 together to form a linear moiety spacer having from 1 through 7 contiguous
 15 atoms to form a ring selected from the group consisting of a cycloalkyl ring
 having from 3 through 8 contiguous members, a cycloalkenyl ring having from
 3 through 8 contiguous members, and a heterocyclyl ring having from 3
 through 8 contiguous members;
 R³⁷ and R³⁸, when bonded to different carbons, are taken together to
 20 form a linear moiety spacer having from 1 through 7 contiguous atoms to form
 a ring selected from the group consisting of a cycloalkyl ring having from 3
 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8
 contiguous members, and a heterocyclyl ring having from 3 through 8
 contiguous members;
 25 R³⁸ and R³⁸, when bonded to different carbons, are taken together to
 form a linear moiety spacer having from 1 through 7 contiguous atoms to form
 a ring selected from the group consisting of a cycloalkyl ring having from 3
 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8
 contiguous members, and a heterocyclyl ring having from 3 through 8
 30 contiguous members;

- R^{37} and R^{38} , when bonded to the same carbon, are taken together to form a group selected from a group consisting of oxo, thiono, alkylene, haloalkylene, and a linear moiety spacer having from 2 through 7 contiguous atoms to form a ring selected from the group consisting of a cycloalkyl ring having from 3 through 8 contiguous members, a cycloalkenyl ring having from 3 through 8 contiguous members, and a heterocyclyl ring having from 3 through 8 contiguous members;

- Y^0 is optionally Q^b-Q^{ss} wherein Q^{ss} is selected from the group consisting of $(CR^{37}R^{38})_f$ wherein f is an integer selected from 1 through 6, $(CH(R^{14}))_c-W^1-(CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 4, and W^1 is selected from the group consisting of W^1 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{14}), (R^{14})NC(O), C(S)N(R^{14}), (R^{14})NC(S), OC(O)N(R^{14}), (R^{14})NC(O)O, SC(S)N(R^{14}), (R^{14})NC(S)S, SC(O)N(R^{14}), (R^{14})NC(O)S, OC(S)N(R^{14}), (R^{14})NC(S)O, N(R^{15})C(O)N(R^{14}), (R^{14})NC(O)N(R^{15}), N(R^{15})C(S)N(R^{14}), (R^{14})NC(S)N(R^{15}), S(O), S(O)₂, S(O)₂N(R^{14}), N(R^{14})S(O)₂, Se, Se(O), Se(O)₂, Se(O)₂N(R^{14}), N(R^{14})Se(O)₂, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^{14}), ON(R^{14}), SiR²⁸R²⁹, and $(CH(R^{14}))_e-W^2-(CH(R^{15}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^2 is selected from the group consisting of $CR^{4a}=CR^{4b}$, ethynylidene (C≡C; 1,2-ethynyl), and $C=CR^{4a}R^{4b}$ with the provisos that R^{14} and R^{15} are selected from other than halo and cyano when directly bonded to N, that $(CR^{37}R^{38})_f$, $(CH(R^{15}))_c$, and $(CH(R^{15}))_e$ are bonded to E^0 , and Q^b is selected from other than

$N(R^{26})N(R^{26})C(NR^{25})N(R^{23})(R^{24})$ or $ON(R^{26})C(NR^{25})N(R^{23})(R^{24})$

when Q^{ss} is $(CR^{37}R^{38})_f$ wherein f is other than the integer 1;

Y^0 is optionally Q^b-Q^{sss} wherein Q^{sss} is $(CH(R^{38}))_r-W^3$, r is an

integer selected from 1 through 3, W^3 is selected from the group consisting of

- 5 1,1-cyclopropyl, 1,2-cyclopropyl, 1,1-cyclobutyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl,
- 10 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-
- 15 3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran-4-one-2,3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hyrido containing nitrogen member of
- 20 the ring of the W^3 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9 , R^{10} , R^{11} , and R^{12} , with the proviso that $(CH(R^{38}))_r$ is bonded to E^0 and Q^b is bonded to lowest numbered substituent position of each W^3 ;

Y^0 is optionally Q^b-Q^{sssr} wherein Q^{sssr} is $(CH(R^{38}))_r-W^4$, r is an

- 25 integer selected from 1 through 3, W^4 is selected from the group consisting of 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl,

- 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran-4-one-2,3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hydrido containing nitrogen member of the ring of the W^4 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9 , R^{10} , R^{11} , and R^{12} , with the provisos that $(CH(R^{38}))_r$ is bonded to E^0 and Q^b is bonded to highest number substituent position of each W^4 ;
- 15 Y^0 is optionally Q^b-Q^{ssss} wherein Q^{ssss} is $(CH(R^{38}))_r-W^5$, r is an integer selected from 1 through 3, W^5 is selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 20 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,4-imidazo(1,2-a)pyridinyl, 2,5-imidazo(1,2-a)pyridinyl, 2,6-imidazo(1,2-a)pyridinyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isindolyl, 1,5-isindolyl, 1,6-isindolyl, 2,4-isindolyl, 2,5-isindolyl, 2,6-isindolyl, 2,7-isindolyl, 1,3-isindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-

naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinoliny, 2,5-quinoliny, 2,6-quinoliny, 2,7-quinoliny, 2,8-quinoliny, 3,4-quinoliny, 3,5-quinoliny, 3,6-quinoliny, 3,7-quinoliny, 3,8-quinoliny, 4,5-quinoliny, 4,6-quinoliny, 4,7-quinoliny, 4,8-quinoliny, 1,4-isoquinoliny, 1,5-isoquinoliny, 1,6-isoquinoliny, 1,7-isoquinoliny, 1,8-isoquinoliny, 3,4-isoquinoliny, 3,5-isoquinoliny, 3,6-isoquinoliny, 3,7-isoquinoliny, 3,8-isoquinoliny, 4,5-isoquinoliny, 4,6-isoquinoliny, 4,7-isoquinoliny, 4,8-isoquinoliny, 3,4-cinnoliny, 3,5-cinnoliny, 3,6-cinnoliny, 3,7-cinnoliny, 3,8-cinnoliny, 4,5-cinnoliny, 4,6-cinnoliny, 4,7-cinnoliny, and 4,8-cinnoliny, and each carbon and hydrido containing nitrogen member of the ring of the W^5 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9 , R^{10} , R^{11} , and R^{12} , with the proviso that Q^b is bonded to lowest number substituent position of each W^5 and that $(CH(R^{38}))_r$ is bonded to E^0 ;

Y^0 is optionally Q^b-Q^{sssr} wherein Q^{sssr} is $(CH(R^{38}))_r-W^6$, r is an integer selected from 1 through 3, W^6 is selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,4-imidazo(1,2-a)pyridinyl, 2,5-imidazo(1,2-a)pyridinyl, 2,6-imidazo(1,2-a)pyridinyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isindolyl, 1,5-isindolyl, 1,6-isindolyl, 2,4-isindolyl, 2,5-isindolyl, 2,6-isindolyl, 2,7-isindolyl, 1,3-isindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl,

- 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinoliny, 2,5-quinoliny, 2,6-quinoliny, 2,7-quinoliny, 2,8-quinoliny, 3,4-quinoliny, 3,5-quinoliny, 3,6-quinoliny, 3,7-quinoliny, 3,8-quinoliny, 4,5-quinoliny, 4,6-quinoliny, 4,7-quinoliny, 4,8-quinoliny, 1,4-isoquinoliny, 1,5-isoquinoliny, 1,6-isoquinoliny, 1,7-isoquinoliny, 1,8-isoquinoliny, 3,4-isoquinoliny, 3,5-isoquinoliny, 3,6-isoquinoliny, 3,7-isoquinoliny, 3,8-isoquinoliny, 4,5-isoquinoliny, 4,6-isoquinoliny, 4,7-isoquinoliny, 4,8-isoquinoliny, 3,4-cinnoliny, 3,5-cinnoliny, 3,6-cinnoliny, 3,7-cinnoliny, 3,8-cinnoliny, 4,5-cinnoliny, 4,6-cinnoliny, 4,7-cinnoliny, and 4,8-cinnoliny, and each carbon and hydrido containing nitrogen member of the ring of the W^6 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9 , R^{10} , R^{11} , and R^{12} , with the proviso that Q^b is bonded to highest number substituent position of each W^6 and that $(CH(R^{38}))_r$ is bonded to E^0 .

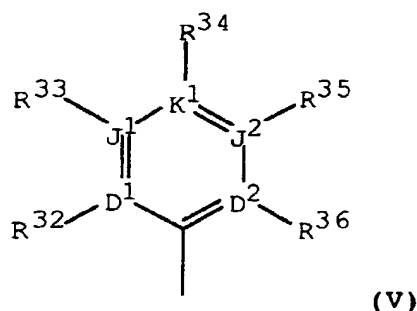
In an embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is selected from the group consisting of O and S;

- J is optionally selected from the group consisting of $CH-R^6$ and $N-R^6$

wherein R^6 is a linear spacer moiety having a chain length of 1 to 4 atoms linked to the point of bonding of a substituent selected from the group consisting of R^{4a} , R^{4b} , R^{39} , R^{40} , R^5 , R^{14} , and R^{15} to form a heterocycl ring having 5 through 8 contiguous members;

- B is formula (V):



wherein D^1 , D^2 , J^1 , J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is O, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is S, one of D^1 , D^2 , J^1 , J^2 and K^1 must be a covalent bond when two of D^1 , D^2 , J^1 , J^2 and K^1 are O and S, and no more than four of D^1 , D^2 , J^1 , J^2 and K^1 are N with the proviso that R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{16} , R^{17} , R^{18} , R^{19} , R^{32} , R^{33} , R^{34} ,

R^{35} , and R^{36} are independently selected from the group consisting of hydrido,

acetamido, haloacetamido, amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aryloxyalkoxy, heterocyclyloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl,

heteroaryl amino, N-heteroaryl amino-N-alkyl amino, heteroaryl aminoalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy,

- halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, alkoxyamino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, 5 arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, 10 arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclisulfonyl, heterocyclisulfinyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower 15 cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, alkylenylamino, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, 20 carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboxy, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl;
- 25 R^{16} , R^{19} , R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;
- R^{32} and R^{33} , R^{33} and R^{34} , R^{34} and R^{35} , and R^{35} and R^{36} are 30 independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through

8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the proviso that no more than one of the group consisting of spacer pairs R^{32} and R^{33} , R^{33} and R^{34} , R^{34} and R^{35} , and R^{35} and R^{36} can be used at the same time;

5 R^9 and R^{10} , R^{10} and R^{11} , R^{11} and R^{12} , and R^{12} and R^{13} are

independently optionally selected to form a spacer pair wherein a spacer pair is taken together to form a linear moiety having from 3 through 6 contiguous atoms connecting the points of bonding of said spacer pair members to form a ring selected from the group consisting of a cycloalkenyl ring having 5 through 8 contiguous members, a partially saturated heterocyclyl ring having 5 through 8 contiguous members, a heteroaryl ring having 5 through 6 contiguous members, and an aryl with the proviso that no more than one of the group consisting of spacer pairs R^9 and R^{10} , R^{10} and R^{11} , R^{11} and R^{12} , and R^{12} and R^{13} can be used at the same time;

15 B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2-C8 alkyl, C3-C8 alkylenyl, C3-C8 alkenyl, C3-C8 alkynyl, C2-C8 haloalkyl, and C3-C8 haloalkenyl wherein each member of group B may be optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

20 B is optionally selected from the group consisting of C3-C15 cycloalkyl, C5-C10 cycloalkenyl, C4-C12 saturated heterocyclyl, and C4-C9 partially saturated heterocyclyl, wherein each ring carbon is optionally substituted with R^{33} , a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon and nitrogen atoms adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen atom adjacent to the R^9 position and two atoms from the point of attachment is optionally

substituted with R^{10} , a ring carbon or nitrogen atom adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12} , a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11} ,
5 a ring carbon or nitrogen atom three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{33} , and a ring carbon or nitrogen atom four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34} ;

A is selected from the group consisting of single covalent bond,
10 $(W^7)_{rr}-(CH(R^{15}))_{pa}$ and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 6, and W^7 is selected from the group consisting of O, S, C(O), C(S), C(O)S, C(S)O, C(O)N(R^7), C(S)N(R^7), (R^7)NC(O), (R^7)NC(S), S(O), S(O)₂, S(O)₂N(R^7), (R^7)NS(O)₂, P(O)(R^8), N(R^7)P(O)(R^8), P(O)(R^8)N(R^7),
15 C(N R^7)N(R^7), (R^7)NC(N R^7), (R^7)NC(N R^7)N R^7 , and N(R^7) with the proviso that no more than one of the group consisting of rr and pa can be 0 at the same time;

R^7 and R^8 are independently selected from the group consisting of hydrido, hydroxy, alkyl, acyl, aroyl, heteroaroyl, and alkoxyalkyl;

20 R^{14} , R^{15} , R^{37} , and R^{38} are independently selected from the group consisting of hydrido, hydroxy, halo, cyano, hydroxyalkyl, alkoxy, alkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, carboxy,
25 carboxyalkyl, carboalkoxy, carboxamide, and carboxamidoalkyl;

R^{14} and R^{38} can be independently selected from the group consisting of acyl, aroyl, and heteroaroyl with the proviso that acyl is selected from other than formyl and 2-oxoacyl;

- Ψ is selected from the group consisting of NR^5 , O, C(O), C(S), S,
 5 S(O), S(O)₂, ON(R^5), P(O)(R^8), and $CR^{39}R^{40}$;

R^5 is selected from the group consisting of hydrido, hydroxy, amino, alkyl, alkoxy, alkoxyalkyl, haloalkyl, acyl, aroyl, and heteroaroyl;

- R^{39} and R^{40} are independently selected from the group consisting of
 10 hydrido, hydroxy, halo, cyano, hydroxyalkyl, acyl, aroyl, heteroaroyl, acylamido, alkoxy, alkyl, alkoxyalkyl, haloalkyl, haloalkoxy, haloalkoxyalkyl, alkylsulfonyl, haloalkylsulfonyl, carboxy, carboxyalkyl, carboalkoxy, carboxamide, and carboxamidoalkyl;

M is selected from the group consisting of N and R^1 -C;

- R^2 and R^1 are independently selected from the group consisting of Z^0 -
 15 Q, hydrido, alkyl, alkenyl, and halo;

- R^1 is optionally selected from the group consisting of amino, aminoalkyl, alkylamino, amidino, guanidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, alkylthio, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, heteroaryl amino, nitro,
 20 arylamino, aralkylamino, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, hydroxyhaloalkyl, cyano, and phosphono;

- Z^0 is selected from the group consisting of covalent single bond, $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 6, $(CH(R^{41}))_g^-$, $W^0-(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0
 25 through 3 and W^0 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R^{41}), (R^{41})NC(O), C(S)N(R^{41}), (R^{41})NC(S), OC(O)N(R^{41}), (R^{41})NC(O)O, SC(S)N(R^{41}), (R^{41})NC(S)S,

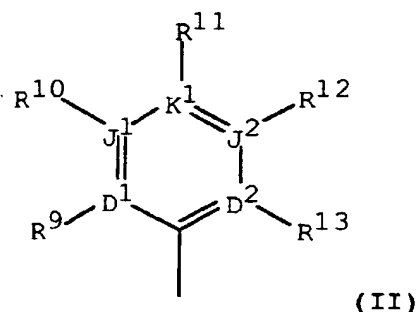
- $\text{SC(O)N(R}^{41}\text{)}, (\text{R}^{41}\text{)NC(O)S, OC(S)N(R}^{41}\text{)}, (\text{R}^{41}\text{)NC(S)O,}$
 $\text{N(R}^{42}\text{)C(O)N(R}^{41}\text{)}, (\text{R}^{41}\text{)NC(O)N(R}^{42}\text{)}, \text{N(R}^{42}\text{)C(S)N(R}^{41}\text{)},$
 $(\text{R}^{41}\text{)NC(S)N(R}^{42}\text{)}, \text{S(O)}, \text{S(O)}_2, \text{S(O)}_2\text{N(R}^{41}\text{)}, \text{N(R}^{41}\text{)S(O)}_2, \text{Se, Se(O)},$
 $\text{Se(O)}_2, \text{Se(O)}_2\text{N(R}^{41}\text{)}, \text{N(R}^{41}\text{)Se(O)}_2, \text{P(O)(R}^8\text{)}, \text{N(R}^7\text{)P(O)(R}^8\text{)},$
 5 $\text{P(O)(R}^8\text{)N(R}^7\text{)}, \text{N(R}^{41}\text{)}, \text{ON(R}^{41}\text{)}, \text{and SiR}^{28}\text{R}^{29}\text{, and } (\text{CH(R}^{41}\text{)})_e\text{-W}^{22}\text{-}$
 $(\text{CH(R}^{42}\text{)})_h$ wherein e and h are integers independently selected from 0
 through 2 and W^{22} is selected from the group consisting of $\text{CR}^{41}=\text{CR}^{42}$,
 $\text{CR}^{41}\text{R}^{42}=\text{C}$; vinylidene), ethynylidene ($\text{C}\equiv\text{C}$; 1,2-ethynyl), 1,2-cyclopropyl,
 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-
 10 cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-
 morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-
 piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl,
 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-
 pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-
 15 pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-
 tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the provisos that R^{41} and
 R^{42} are selected from other than halo and cyano when directly bonded to N
 and Z^0 is directly bonded to the pyrimidinone ring:
 R^{41} and R^{42} are independently selected from the group consisting of
 20 amidino, hydroxyamino, hydrido, hydroxy, amino, halo, cyano, aryloxy,
 hydroxyalkyl, acyl, aroyl, heteroaroyl, heteroaryloxyalkyl, alkoxy, alkyl, aryl,
 aralkyl, aryloxyalkyl, aralkoxyalkylalkoxy, alkoxyalkyl, heteroaryloxyalkyl,
 cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl,
 haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxy,
 25 haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl,
 halocycloalkenyloxyalkyl, saturated heterocyclyl, partially saturated
 heterocyclyl, heteroaryl, heteroaralkyl, heteroarylthioalkyl,
 heteroaralkylthioalkyl, alkylsulfonyl, haloalkylsulfonyl, arylsulfonyl,

WO 00/69832

PCT/US00/09806

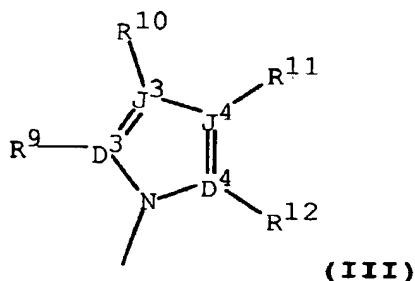
arylsulfonylalkyl, aralkylsulfonyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfonyl, and aralkylsulfonylalkyl;

Q is formula (II):



- 5 wherein D^1 , D^2 , J^1 , J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is O, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is S, one of D^1 , D^2 , J^1 , J^2 and K^1 must be a covalent bond when two of D^1 , D^2 , J^1 , J^2 and K^1 are O and S,
- 10 and no more than four of D^1 , D^2 , J^1 , J^2 and K^1 are N, with the proviso that R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

Q is optionally selected from formula (III):



- 15 wherein D^3 , D^4 , J^3 , and J^4 are independently selected from the group consisting of C, N, O, and S, no more than one of D^3 , D^4 , J^3 , and J^4 is O, no

more than one of D^3 , D^4 , J^3 , and J^4 is S, and no more than three of D^1 , D^2 , J^1 , and J^2 are N with the proviso that R^9 , R^{10} , R^{11} , and R^{12} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

5 Q is optionally selected from the group consisting of hydrido, alkyl, alkoxy, alkylamino, alkylthio, haloalkylthio, alkenyl, alkynyl, saturated heterocyclyl, partially saturated heterocyclyl, acyl, aroyl, heteroaroyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkylalkenyl, 10 haloalkyl, haloalkoxy, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, and halocycloalkenyloxyalkyl with the proviso that Z^0 is selected from other than a single covalent bond when Q is hydrido;

K is $(CR^{4a}R^{4b})_n$ wherein n is an integer selected from 1 through 2;

15 R^{4a} and R^{4b} are independently selected from the group consisting of halo, hydrido, hydroxy, cyano, hydroxyalkyl, alkyl, alkenyl, alkoxyalkyl, aralkyl, heteroaralkyl, alkylthioalkyl, haloalkyl, haloalkenyl, and cyanoalkyl;

E^0 is E^1 , when K is $(CR^{4a}R^{4b})_n$, wherein E^1 is selected from the group consisting of a covalent single bond, O, S, C(O), C(S), C(O)O, C(S)O, 20 C(O)S, C(S)S, C(O)N(R^7), (R^7)NC(O), C(S)N(R^7), (R^7)NC(S), OC(O)N(R^7), (R^7)NC(O)O, SC(S)N(R^7), (R^7)NC(S)S, SC(O)N(R^7), (R^7)NC(O)S, OC(S)N(R^7), (R^7)NC(S)O, N(R^8)C(O)N(R^7), (R^7)NC(O)N(R^8), N(R^8)C(S)N(R^7), (R^7)NC(S)N(R^8), S(O), S(O)₂, S(O)₂N(R^7), N(R^7)S(O)₂, S(O)₂N(R^7)C(O), C(O)N(R^7)S(O)₂, P(O)(R^8), 25 N(R^7)P(O)(R^8), P(O)(R^8)N(R^7), N(R^7), ON(R^7), $CR^{4a}=CR^{4b}$, ethynylidene (C=C; 1,2-ethynyl), and $C=CR^{4a}R^{4b}$;

K is optionally $(\text{CH}(\text{R}^{14}))_j\text{-T}$ wherein j is selected from a integer from 0 through 2 and T is selected from the group consisting of single covalent bond, O, S, and $\text{N}(\text{R}^7)$ with the proviso that $(\text{CH}(\text{R}^{14}))_j$ is bonded to the pyrimidinone ring;

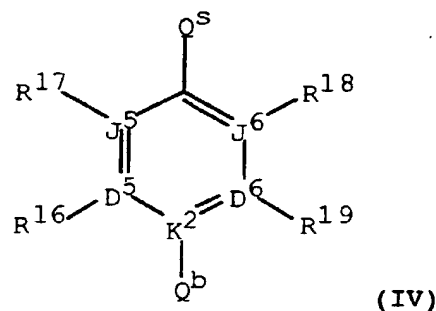
- 5 E^0 is optionally E^2 , when K is $(\text{CH}(\text{R}^{14}))_j\text{-T}$, wherein E^2 is selected from the group consisting of a covalent single bond, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O) $\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{O})$, C(S) $\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{S})$, $(\text{R}^7)\text{NC}(\text{O})\text{O}$, $(\text{R}^7)\text{NC}(\text{S})\text{S}$, $(\text{R}^7)\text{NC}(\text{O})\text{S}$, $(\text{R}^7)\text{NC}(\text{S})\text{O}$, $\text{N}(\text{R}^8)\text{C}(\text{O})\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{O})\text{N}(\text{R}^8)$, $\text{N}(\text{R}^8)\text{C}(\text{S})\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{S})\text{N}(\text{R}^8)$, S(O), S(O)₂,
 10 S(O)₂ $\text{N}(\text{R}^7)$, $\text{N}(\text{R}^7)\text{S}(\text{O})_2$, S(O)₂N(H)C(O), C(O)N(H)S(O)₂, P(O)(R⁸), $\text{N}(\text{R}^7)\text{P}(\text{O})(\text{R}^8)$, P(O)(R⁸) $\text{N}(\text{R}^7)$, and $\text{N}(\text{R}^7)$;

- K is optionally G- $(\text{CH}(\text{R}^{15}))_k$ wherein k is selected from an integer from 1 through 2 and G is selected from the group consisting of O, S, and $\text{N}(\text{R}^7)$ with the proviso that R^{15} is other than hydroxy, cyano, halo, amino,
 15 alkylamino, dialkylamino, and sulfhydryl when k is 1;

- E^0 is optionally E^3 when K is G- $(\text{CH}(\text{R}^{15}))_k$, wherein E^3 is selected from the group consisting of a covalent single bond, O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O) $\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{O})$, C(S) $\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{S})$, OC(O) $\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{O})\text{O}$, SC(S) $\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{S})\text{S}$,
 20 SC(O) $\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{O})\text{S}$, OC(S) $\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{S})\text{O}$, $\text{N}(\text{R}^8)\text{C}(\text{O})\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{O})\text{N}(\text{R}^8)$, $\text{N}(\text{R}^8)\text{C}(\text{S})\text{N}(\text{R}^7)$, $(\text{R}^7)\text{NC}(\text{S})\text{N}(\text{R}^8)$, S(O), S(O)₂, S(O)₂ $\text{N}(\text{R}^7)$, $\text{N}(\text{R}^7)\text{S}(\text{O})_2$, P(O)(R⁸), $\text{N}(\text{R}^7)\text{P}(\text{O})(\text{R}^8)$, P(O)(R⁸) $\text{N}(\text{R}^7)$,

$N(R^7)$, $ON(R^7)$, $CR^{4a}=CR^{4b}$, ethynylidene ($C\equiv C$; 1,2-ethynyl), and $C=CR^{4a}R^{4b}$;

Y^0 is formula (IV):



- 5 wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is independently selected from the group consisting of C and N^+ , no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a
- 10 covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, no more than three of D^5 , D^6 , J^5 , and J^6 is N when K^2 is N^+ , and no more than four of D^5 , D^6 , J^5 , and J^6 are N when K^2 is carbon with the provisos that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the
- 15 divalent nature of oxygen;
- R^{16} and R^{17} are optionally independently taken together to form a linear moiety spacer having from 3 through 6 contiguous atoms connected to form a ring selected from the group consisting of a cycloalkenyl ring having from 5 through 8 contiguous members, a partially saturated heterocyclyl ring
- 20 having from 5 through 8 contiguous members, a heteroaryl having from 5 through 6 contiguous members, and an aryl;

- Q^b is selected from the group consisting of $NR^{20}R^{21}$,
 $+NR^{20}R^{21}R^{22}$, oxy, alkyl, aminoalkylenyl, alkylamino, dialkylamino,
dialkylsulfoniumalkyl, acylamino and Q^{be} , wherein Q^{be} is hydrido and R^{20} ,
 R^{21} , and R^{22} are independently selected from the group consisting of hydrido,
5 amino, alkyl, hydroxy, alkoxy, aminoalkylenyl, alkylamino, dialkylamino, and
hydroxyalkyl with the provisos that no more than one of R^{20} , R^{21} , and R^{22} is
hydroxy, alkoxy, alkylamino, amino, and dialkylamino at the same time and
that R^{20} , R^{21} , and R^{22} must be other than be hydroxy, alkoxy, alkylamino,
amino, and dialkylamino when K^2 is N^+ ;
10 R^{20} and R^{21} , R^{20} and R^{22} , and R^{21} and R^{22} are independently
optionally selected to form a spacer pair wherein a spacer pair is taken together
to form a linear moiety having from 4 through 7 contiguous atoms connecting
the points of bonding of said spacer pair members to form a heterocyclyl ring
having 5 through 8 contiguous members with the proviso that no more than
15 one of the group consisting of spacer pairs R^{20} and R^{21} , R^{20} and R^{22} , and
 R^{21} and R^{22} is used at the same time;

- Q^b is optionally selected from the group consisting of
 $N(R^{26})SO_2N(R^{23})(R^{24})$, $N(R^{26})C(O)OR^5$, $N(R^{26})C(O)SR^5$,
 $N(R^{26})C(S)OR^5$ and $N(R^{26})C(S)SR^5$ with the proviso that no more than one
20 of R^{23} , R^{24} , and R^{26} is hydroxy, alkoxy, alkylamino, amino, and
dialkylamino when two of the group consisting of R^{23} , R^{24} , and R^{26} are
bonded to the same atom;

Q^b is optionally selected from the group consisting of
dialkylsulfonium, trialkylphosphonium, $C(NR^{25})NR^{23}R^{24}$,

- $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $N(R^{26})C(O)N(R^{23})(R^{24})$,
 $N(R^{26})C(S)N(R^{23})(R^{24})$, $C(NR^{25})OR^5$,
 $C(O)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $C(S)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$,
 $N(R^{26})N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $ON(R^{26})C(NR^{25})N(R^{23})(R^{24})$,
5 $N(R^{26})N(R^{26})SO_2N(R^{23})(R^{24})$, $C(NR^{25})SR^5$, $C(O)NR^{23}R^{24}$, and
 $C(O)NR^{23}R^{24}$ with the provisos that no more than one of R^{23} , R^{24} , and R^{26}
can be hydroxy, alkoxy, alkylaminol, amino, or dialkylamino when two of the
group consisting of R^{23} , R^{24} , and R^{26} are bonded to the same atom and that
said Q^b group is bonded directly to a carbon atom;
- 10 R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group
consisting of hydrido, alkyl, hydroxy, alkoxy, aminoalkylenyl, alkylamino,
dialkylamino, amino, and hydroxyalkyl;
 R^{23} and R^{24} are optionally taken together to form a linear spacer moiety
having from 4 through 7 contiguous atoms connecting the points of bonding to
15 form a heterocyclcyl ring having 5 through 8 contiguous members;
- Q^s is selected from the group consisting of a single covalent bond,
 $(CR^{37}R^{38})_b(W^0)_{az}$ wherein az is an integer selected from 0 through 1, b is
an integer selected from 1 through 4, and W^0 is selected from the group
consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R¹⁴),
20 (R¹⁴)NC(O), C(S)N(R¹⁴), (R¹⁴)NC(S), OC(O)N(R¹⁴), SC(S)N(R¹⁴),
SC(O)N(R¹⁴), OC(S)N(R¹⁴), N(R¹⁵)C(O)N(R¹⁴), (R¹⁴)NC(O)N(R¹⁵),
N(R¹⁵)C(S)N(R¹⁴), (R¹⁴)NC(S)N(R¹⁵), S(O), S(O)₂, S(O)₂N(R¹⁴),
N(R¹⁴)S(O)₂, P(O)(R⁸), N(R⁷)P(O)(R⁸), P(O)(R⁸)N(R⁷), N(R¹⁴),

WO 00/69832

PCT/US00/09806

$\text{ON}(\text{R}^{14})$, $(\text{CH}(\text{R}^{14}))_c\text{-W}^1\text{-(CH}(\text{R}^{15}))_d$ wherein c and d are integers

independently selected from 1 through 4, and W^1 is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R¹⁴),

$(\text{R}^{14})\text{NC(O)}$, $\text{C(S)N(R}^{14})$, $(\text{R}^{14})\text{NC(S)}$, $\text{OC(O)N(R}^{14})$, $(\text{R}^{14})\text{NC(O)O}$,

5 $\text{SC(S)N(R}^{14})$, $(\text{R}^{14})\text{NC(S)S}$, $\text{SC(O)N(R}^{14})$, $(\text{R}^{14})\text{NC(O)S}$, $\text{OC(S)N(R}^{14})$,

$(\text{R}^{14})\text{NC(S)O}$, $\text{N(R}^{15})\text{C(O)N(R}^{14})$, $(\text{R}^{14})\text{NC(O)N(R}^{15})$,

$\text{N(R}^{15})\text{C(S)N(R}^{14})$, $(\text{R}^{14})\text{NC(S)N(R}^{15})$, S(O), S(O)₂, S(O)₂N(R¹⁴),

$\text{N(R}^{14})\text{S(O)}_2$, $\text{P(O)(R}^8)$, $\text{N(R}^7)\text{P(O)(R}^8)$, $\text{P(O)(R}^8)\text{N(R}^7)$, $\text{N(R}^{14})$,

$\text{ON(R}^{14})$, and $(\text{CH}(\text{R}^{14}))_e\text{-W}^{22}\text{-(CH}(\text{R}^{15}))_h$ wherein e and h are integers

10 independently selected from 0 through 2 and W^{22} is selected from the group

consisting of $\text{CR}^{41}=\text{CR}^{42}$, $\text{CR}^{41}\text{R}^{42}=\text{C}$; vinylidene), ethynylidene ($\text{C}\equiv\text{C}$;

1,2-ethynyl), 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-

cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-

morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-

15 piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl,

1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-

piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-

pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-

tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the

20 provisos that R^{14} and R^{15} are selected from other than halo and cyano when

directly bonded to N and that $(\text{CR}^{37}\text{R}^{38})_b$, $(\text{CH}(\text{R}^{14}))_c$, $(\text{CH}(\text{R}^{14}))_e$ and are

bonded to E^0 ;

Y^0 is optionally $\text{Q}^b\text{-Q}^{\text{ss}}$ wherein Q^{ss} is selected from the group

consisting of $(\text{CR}^{37}\text{R}^{38})_f$ wherein f is an integer selected from 1 through 6,

- (CH(R¹⁴))_c-W¹-(CH(R¹⁵))_d wherein c and d are integers independently selected from 1 through 4, and W¹ is selected from the group consisting of W¹ is selected from the group consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R¹⁴), (R¹⁴)NC(O), C(S)N(R¹⁴), (R¹⁴)NC(S),
- 5 OC(O)N(R¹⁴), (R¹⁴)NC(O)O, SC(S)N(R¹⁴), (R¹⁴)NC(S)S, SC(O)N(R¹⁴), (R¹⁴)NC(O)S, OC(S)N(R¹⁴), (R¹⁴)NC(S)O, N(R¹⁵)C(O)N(R¹⁴), (R¹⁴)NC(O)N(R¹⁵), N(R¹⁵)C(S)N(R¹⁴), (R¹⁴)NC(S)N(R¹⁵), S(O), S(O)₂, S(O)₂N(R¹⁴), N(R¹⁴)S(O)₂, P(O)(R⁸), N(R⁷)P(O)(R⁸), P(O)(R⁸)N(R⁷), N(R¹⁴), ON(R¹⁴), and (CH(R¹⁴))_e-W²-(CH(R¹⁵))_h
- 10 wherein e and h are integers independently selected from 0 through 2 and W² is selected from the group consisting of CR^{4a}=CR^{4b}, ethynylidene (C≡C; 1,2-ethynyl), and C=CR^{4a}R^{4b} with the provisos that R¹⁴ and R¹⁵ are selected from other than halo and cyano when directly bonded to N and that (CR³⁷R³⁸)_f, (CH(R¹⁴))_c, and (CH(R¹⁴))_e are bonded to E⁰;
- 15 Y⁰ is optionally Q^b-Q^{sss} wherein Q^{sss} is (CH(R³⁸))_r-W³, r is an integer selected from 1 through 3, W³ is selected from the group consisting of 1,1-cyclopropyl, 1,2-cyclopropyl, 1,1-cyclobutyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-
- 20 morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-
- 25 pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-

- pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran-4-one-2,3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hydrido containing nitrogen member of the ring of the W^3 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9 , R^{10} , R^{11} , and R^{12} , with the proviso that $(CH(R^{38}))_r$ is bonded to E^0 and Q^b is bonded to lowest numbered substituent position of each W^3 ;
- Y^0 is optionally Q^b-Q^{sssr} wherein Q^{sssr} is $(CH(R^{38}))_r-W^4$, r is an integer selected from 1 through 3, W^4 is selected from the group consisting of 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran-4-one-2,3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hydrido containing nitrogen member of the ring of the W^4 other than the points of attachment is optionally substituted with one or more of the group consisting of

R^9 , R^{10} , R^{11} , and R^{12} , with the provisos that $(CH(R^{38}))_r$ is bonded to E^0

and Q^b is bonded to highest number substituent position of each W^4 ;

Y^0 is optionally Q^b-Q^{ssss} wherein Q^{ssss} is $(CH(R^{38}))_r-W^5$, r is an

integer selected from 1 through 3, W^5 is selected from the group consisting of

- 5 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-
- 10 benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-
- 15 isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl,
- 20 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-
- 25 isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4-cinnolinyl, 3,5-cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hydrido
- 30 containing nitrogen member of the ring of the W^5 other than the points of attachment is optionally substituted with one or more of the group consisting of

R^9 , R^{10} , R^{11} , and R^{12} , with the proviso that Q^b is bonded to lowest number substituent position of each W^5 and that $(CH(R^{38}))_r$ is bonded to E^0 ;

Y^0 is optionally Q^b-Q^{sssr} wherein Q^{sssr} is $(CH(R^{38}))_r-W^6$, r is an

integer selected from 1 through 3, W^6 is selected from the group consisting of

- 5 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-
- 10 benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-
- 15 indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-
- 20 benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-
- 25 naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-
- 30 quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4-cinnolinyl, 3,5-
- cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hydrido
- containing nitrogen member of the ring of the W^6 other than the points of
- attachment is optionally substituted with one or more of the group consisting of

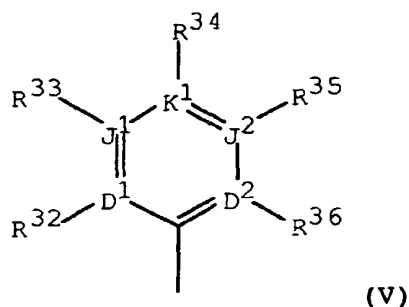
WO 00/69832

PCT/US00/09806

R^9 , R^{10} , R^{11} , and R^{12} , with the proviso that Q^b is bonded to highest number substituent position of each W^6 and that $(CH(R^{38}))_r$ is bonded to E^0 .

In another embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

- 5 J is selected from the group consisting of O and S;
B is formula (V):



- wherein D^1 , D^2 , J^1 , J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is O,
10 no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is S, one of D^1 , D^2 , J^1 , J^2 and K^1 must be a covalent bond when two of D^1 , D^2 , J^1 , J^2 and K^1 are O and S, and no more than four of D^1 , D^2 , J^1 , J^2 and K^1 are N;

R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{16} , R^{17} , R^{18} , R^{19} , R^{32} , R^{33} , R^{34} ,

- 15 R^{35} , and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, carboxy, heteroaralkylthio, heteroaralkoxy, cycloalkylamino, acylalkyl, acylalkoxy, aryloylalkoxy, heterocycloxy, aralkylaryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl,
20 perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl,

heteroaryl amino, N-heteroaryl amino-N-alkyl amino, heteroaryl amino alkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, 5 halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, alkoxyamino, thio, nitro, lower alkyl amino, alkylthio, alkylthioalkyl, aryl amino, aralkyl amino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, 10 alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, 15 heteroarylsulfonyl, heterocyclisulfonyl, heterocyclylthio, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, 20 hydroxyaralkyl, hydroxyalkyl, alkylenyl amino, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarboxamido, alkylamidocarbonylamido, 25 arylamidocarbonylamido, carboalkoxyalkyl, carboalkoxyalkenyl, carboxy, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl;

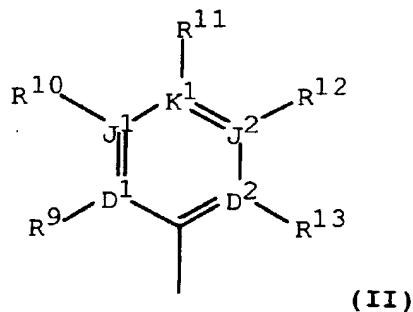
R^{16} , R^{19} , R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently optionally

30 Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2-C8 alkyl, C3-C8 alkylenyl, C3-C8 alkenyl, C3-C8 alkynyl,

- is selected from the group consisting of O, S, C(O), C(O)N(R⁷), C(S)N(R⁷), (R⁷)NC(O), (R⁷)NC(S), and N(R⁷) with the proviso that no more than one of the group consisting of *rr* and *pa* can be 0 at the same time;
- R⁷ and R⁸ are independently selected from the group consisting of
- 5 hydrido, hydroxy, alkyl, and alkoxyalkyl;
- R¹⁴, R¹⁵, R³⁷, and R³⁸ are independently selected from the group consisting of hydrido, hydroxy, halo, alkyl, alkoxyalkyl, haloalkyl, haloalkoxy, and haloalkoxyalkyl;
- R¹⁴ and R³⁸ can be independently selected from the group consisting
- 10 of aroyl and heteroaroyl;
- Ψ is selected from the group consisting of NR⁵, C(O), and S(O)₂;
- R⁵ is selected from the group consisting of hydrido, hydroxy, alkyl, and alkoxy;
- R³⁹ and R⁴⁰ are independently selected from the group consisting of
- 15 hydrido, hydroxy, halo, hydroxyalkyl, alkyl, alkoxyalkyl, haloalkyl, haloalkoxy, and haloalkoxyalkyl;
- M is selected from the group consisting of N and R¹-C;
- R¹ is selected from the group consisting of hydrido, alkyl, alkenyl, cyano, halo, haloalkyl, haloalkoxy, haloalkylthio, amino, aminoalkyl,
- 20 alkylamino, amidino, guanidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, alkylthio, and phosphono;
- R² is Z⁰-Q;
- Z⁰ is selected from the group consisting of covalent single bond, (CR⁴¹R⁴²)_q wherein *q* is an integer selected from 1 through 3, (CH(R⁴¹))_g-
- 25 W⁰-(CH(R⁴²))_p wherein *g* and *p* are integers independently selected from 0 through 3 and W⁰ is selected from the group consisting of O, S, C(O), S(O),

- $S(O)_2$, $N(R^{41})$, and $ON(R^{41})$, and $(CH(R^{41}))_e-W^{22}-(CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 2 and W^{22} is selected from the group consisting of $CR^{41}=CR^{42}$, 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the proviso that Z^0 is directly bonded to the pyrimidinone ring;
- R^{41} and R^{42} are independently selected from the group consisting of amidino, hydroxyamino, hydrido, hydroxy, amino, and alkyl;
- Q is selected from the group consisting of hydrido, with the proviso that Z^0 is other than a covalent single bond, the formula (II):



- wherein D^1 , D^2 , J^1 , J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is O, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is S, one of D^1 , D^2 , J^1 , J^2 and K^1 must be a covalent bond when two of D^1 , D^2 , J^1 , J^2 and K^1 are O and S,

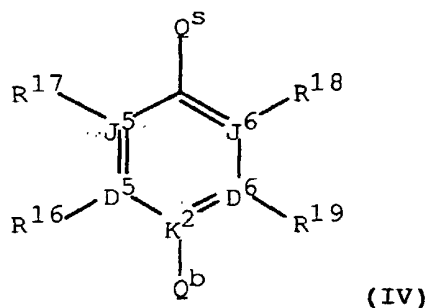
WO 00/69832

PCT/US00/09806

and no more than four of D^1 , D^2 , J^1 , J^2 and K^1 is N, with the proviso that R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

- 5 K is $(CR^{4a}R^{4b})_n$ wherein n is an integer selected from 1 through 2;
 R^{4a} and R^{4b} are independently selected from the group consisting of halo, hydrido, hydroxyalkyl, alkyl, alkoxyalkyl, alkylthioalkyl, and haloalkyl;
 E^0 is selected from the group consisting of a covalent single bond,
 $C(O)$, $C(S)$, $C(O)N(R^7)$, $(R^7)NC(O)$, $S(O)_2$, $(R^7)NS(O)_2$, and $S(O)_2N(R^7)$;

- 10 Y^0 is formula (IV):



- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N when K^2 is carbon with the provisos that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- 20

- Q^b is selected from the group consisting of $NR^{20}R^{21}$,
 $+NR^{20}R^{21}R^{22}$, aminoalkylenyl, and Q^{be} , wherein Q^{be} is hydrido and R^{20} ,
 R^{21} , and R^{22} are independently selected from the group consisting of hydrido,
 alkyl, hydroxy, amino, aminoalkylenyl, dialkylamino, alkylamino, and
 5 hydroxyalkyl with the proviso that no more than one of R^{20} and R^{21} is
 hydroxy, amino, alkylamino, or dialkylamino at the same time;

- Q^b is optionally selected from the group consisting of
 $C(NR^{25})NR^{23}R^{24}$, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$,
 $C(O)N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, $N(R^{26})N(R^{26})C(NR^{25})N(R^{23})(R^{24})$,
 10 and $ON(R^{26})C(NR^{25})N(R^{23})(R^{24})$ with the provisos that no more than one
 of R^{23} , R^{24} , and R^{26} is hydroxy, alkylamino, amino, or dialkylamino when
 two of the group consisting of R^{23} , R^{24} , and R^{26} are bonded to the same
 atom;

- R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group
 15 consisting of hydrido, alkyl, hydroxy, amino, alkylenylamino, dialkylamino,
 alkylamino, and hydroxyalkyl;

- Q^s is selected from the group consisting of a single covalent bond,
 $(CR^{37}R^{38})_b(W^0)_{az}$ wherein az is an integer selected from 0 through 1, b is
 an integer selected from 1 through 5, and W^0 is selected from the group
 20 consisting of O, C(O), S(O), S(O)₂, S(O)₂N(R¹⁴), N(R¹⁴)S(O)₂, and
 $N(R^{14})$, $(CH(R^{14}))_c-W^1-(CH(R^{15}))_d$ wherein c and d are integers
 independently selected from 1 through 4 and W^1 is selected from the group
 consisting of O, S, C(O), C(S), C(O)O, C(S)O, C(O)S, C(S)S, C(O)N(R¹⁴),

- $(R^{14})NC(O)$, $C(S)N(R^{14})$, $(R^{14})NC(S)$, $OC(O)N(R^{14})$, $(R^{14})NC(O)O$,
 $SC(S)N(R^{14})$, $(R^{14})NC(S)S$, $SC(O)N(R^{14})$, $(R^{14})NC(O)S$, $OC(S)N(R^{14})$,
 $(R^{14})NC(S)O$, $N(R^{15})C(O)N(R^{14})$, $(R^{14})NC(O)N(R^{15})$,
 $N(R^{15})C(S)N(R^{14})$, $(R^{14})NC(S)N(R^{15})$, $S(O)$, $S(O)_2$, $S(O)_2N(R^{14})$,
5 $N(R^{14})S(O)_2$, $P(O)(R^8)$, $N(R^7)P(O)(R^8)$, $P(O)(R^8)N(R^7)$, $N(R^{14})$,
 $ON(R^{14})$, and $(CH(R^{14}))_e-W^{22}-(CH(R^{15}))_h$ wherein e and h are integers
independently selected from 0 through 2 and W^{22} is selected from the group
consisting of $CR^{41}=CR^{42}$, $CR^{41}R^{42}=C$; vinylidene), ethynylidene ($C\equiv C$;
1,2-ethynyl), 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-
10 cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-
morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-
piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl,
1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-
15 piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-
pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-
tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the
provisos that R^{14} and R^{15} are selected from other than halo and cyano when
directly bonded to N and that $(CR^{37}R^{38})_b$, $(CH(R^{14}))_c$, and $(CH(R^{14}))_e$ are
bonded to E^0 ;
20 Y^0 is optionally Q^b-Q^{ss} wherein Q^{ss} is selected from the group
consisting of $(CR^{37}R^{38})_f$ wherein f is an integer selected from 1 through 4,
 $(CH(R^{14}))_c-W^1-(CH(R^{15}))_d$ wherein c and d are integers independently
selected from 1 through 2, and W^1 is selected from the group consisting of W^1
is selected from the group consisting of O, S, C(O), C(O)N(R¹⁴),

- (R¹⁴)NC(O), N(R¹⁵)C(O)N(R¹⁴), (R¹⁴)NC(O)N(R¹⁵), N(R¹⁴), ON(R¹⁴), and (CH(R¹⁴))_e-W²-(CH(R¹⁵))_h wherein e and h are integers independently selected from 0 through 2 and W² is selected from the group consisting of CR^{4a}=CR^{4b}, ethynylidene (C≡C; 1,2-ethynyl), and C=CR^{4a}R^{4b} with the
- 5 provisos that R¹⁴ and R¹⁵ are selected from other than halo when directly bonded to N and that (CR³⁷R³⁸)_f, (CH(R¹⁴))_c, and (CH(R¹⁴))_e are bonded to E⁰;

- Y⁰ is optionally Q^b-Q^{sss} wherein Q^{sss} is (CH(R³⁸))_r-W³, r is an integer selected from 1 through 2, W³ is selected from the group consisting of
- 10 1,1-cyclopropyl, 1,2-cyclopropyl, 1,1-cyclobutyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl,
- 15 1,3-piperidinyl, 1,4-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-
- 20 3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran-4-one-2,3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hyrido containing nitrogen member of
- 25 the ring of the W³ other than the points of attachment is optionally substituted with one or more of the group consisting of R⁹, R¹⁰, R¹¹, and R¹², with the

proviso that $(\text{CH}(\text{R}^{38}))_r$ is bonded to E^0 and Q^b is bonded to lowest numbered substituent position of each W^3 ;

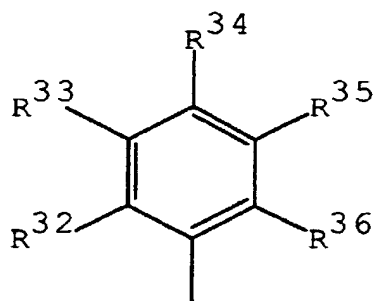
- Y^0 is optionally $\text{Q}^b\text{-Q}^{\text{sssr}}$ wherein Q^{sssr} is $(\text{CH}(\text{R}^{38}))_r\text{-W}^4$, r is an integer selected from 1 through 2, W^4 is selected from the group consisting of
- 5 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,4-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,5-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 1,4-piperazinyl, 2,3-piperazinyl, 2,5-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 1,4-piperidinyl, 2,3-
 - 10 piperidinyl, 2,4-piperidinyl, 2,5-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 3,5-piperidinyl, 3,6-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2H-2,3-pyranyl, 2H-2,4-pyranyl, 2H-2,5-pyranyl, 4H-2,3-pyranyl, 4H-2,4-pyranyl, 4H-2,5-pyranyl, 2H-pyran-2-one-3,4-yl, 2H-pyran-2-one-4,5-yl, 4H-pyran-
 - 15 4-one-2,3-yl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, 3,4-tetrahydrofuranyl, 2,3-tetrahydropyranyl, 2,4-tetrahydropyranyl, 2,5-tetrahydropyranyl, 2,6-tetrahydropyranyl, 3,4-tetrahydropyranyl, and 3,5-tetrahydropyranyl, and each carbon and hyrido containing nitrogen member of the ring of the W^4 other than the points of
 - 20 attachment is optionally substituted with one or more of the group consisting of R^9 , R^{10} , R^{11} , and R^{12} , with the provisos that $(\text{CH}(\text{R}^{38}))_r$ is bonded to E^0 and Q^b is bonded to highest number substituent position of each W^4 ;

- Y^0 is optionally $\text{Q}^b\text{-Q}^{\text{ssss}}$ wherein Q^{ssss} is $(\text{CH}(\text{R}^{38}))_r\text{-W}^5$, r is an integer selected from 1 through 2, W^5 is selected from the group consisting of
- 25 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-

- benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-
 benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-
 imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-
 a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-
 5 indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-
 isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-
 isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-
 indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-
 benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-
 10 benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl,
 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-
 naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-
 quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-
 quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-
 15 quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-
 isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-
 isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-
 isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4-cinnolinyl, 3,5-
 cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-
 20 cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hyrido
 containing nitrogen member of the ring of the W^5 other than the points of
 attachment is optionally substituted with one or more of the group consisting of
 R^9 , R^{10} , R^{11} , and R^{12} , with the proviso that Q^b is bonded to lowest number
 substituent position of each W^5 and that $(CH(R^{38}))_r$ is bonded to E^0 ;
 25 Y^0 is optionally Q^b-Q^{sssr} wherein Q^{sssr} is $(CH(R^{38}))_r-W^6$, r is an
 integer selected from 1 through 2, W^6 is selected from the group consisting of
 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl,
 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl,
 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl,
 30 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl,
 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-
 benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-

- benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4-cinnolinyl, 3,5-cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hyrido
- containing nitrogen member of the ring of the W^6 other than the points of attachment is optionally substituted with one or more of the group consisting of R^9 , R^{10} , R^{11} , and R^{12} , with the proviso that Q^b is bonded to highest number substituent position of each W^6 and that $(CH(R^{38}))_r$ is bonded to E^0 .

- In a preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,
- J is O;
- B is the Formula:



$R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{32}, R^{33}, R^{34}, R^{35},$ and R^{36} are

- independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkylenedioxy, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, hydroxy, amino, alkoxyamino, nitro, lower alkylamino, alkylthio, alkylthioalkyl, alkylsulfinyl, alkylsulfonyl, alkylsulfonylalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkanoyl, haloalkanoyl, alkyl, alkenyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyalkyl, aminoalkyl, haloalkoxyalkyl, carboxyalkyl, carboalkoxy, carboxy, carboxamido, carboxamidoalkyl, and cyano;

- $R^9, R^{10}, R^{11}, R^{12},$ and R^{13} are optionally selected from the group consisting of heteroaryl and heterocyclyl with the proviso that $R^9, R^{10}, R^{11}, R^{12},$ and R^{13} are substituents for other than B;

$R^{16}, R^{19}, R^{32}, R^{33}, R^{34}, R^{35},$ and R^{36} are independently optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

- B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2-C8 alkyl, C3-C8 alkylenyl, C3-C8 alkenyl, C3-C8 alkynyl, and C2-C8 haloalkyl, wherein each member of group B may be optionally substituted at any carbon up to and including 6 atoms from the point of

attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

- B is selected from the group consisting of C3-C12 cycloalkyl and C4-heterocyclyl, wherein each ring carbon may be optionally substituted with R^{33} ,
- 5 a ring carbon other than the ring carbon at the point of attachment of B to A may be optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbons and a nitrogen adjacent to the carbon at the point of attachment may be optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two
- 10 atoms from the point of attachment may be substituted with R^{10} , a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment may be substituted with R^{12} , a ring carbon or nitrogen three atoms from the point of attachment and adjacent to the R^{10} position may be substituted with R^{11} , a ring carbon or nitrogen three atoms from the point of
- 15 attachment and adjacent to the R^{12} position may be substituted with R^{33} , and a ring carbon or nitrogen four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions may be substituted with R^{34} ;

- A is selected from the group consisting of single covalent bond, $(W^7)_{rr}-(CH(R^{15}))_{pa}$ and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer
- 20 selected from 0 through 1, pa is an integer selected from 0 through 6, and W^7 is selected from the group consisting of O, S, C(O), $(R^7)NC(O)$, $(R^7)NC(S)$, and $N(R^7)$ with the proviso that no more than one of the group consisting of rr and pa is 0 at the same time;

- R^7 is selected from the group consisting of hydrido, hydroxy, and
- 25 alkyl;

R^{15} is selected from the group consisting of hydrido, hydroxy, halo, alkyl, and haloalkyl;

Ψ is selected from the group consisting of NH and NOH;

M is selected from the group consisting of N and R^1 -C;

5 R^1 is selected from the group consisting of hydrido, alkyl, alkenyl, cyano, halo, haloalkyl, haloalkoxy, haloalkylthio, amino, aminoalkyl, alkylamino, amidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, and alkylthio;

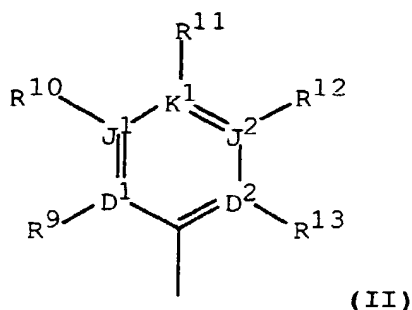
R^2 is Z^0 -Q;

10 Z^0 is selected from the group consisting of covalent single bond, $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 3, $(CH(R^{41}))_g$ - W^0 -($CH(R^{42}))_p$ wherein g and p are integers independently selected from 0 through 3 and W^0 is selected from the group consisting of O, S, C(O), S(O), $N(R^{41})$, and $ON(R^{41})$, and $(CH(R^{41}))_e$ - W^{22} -($CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 1 and W^{22} is selected from the group consisting of $CR^{41}=CR^{42}$, 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the proviso that Z^0 is directly bonded to the

20 pyrimidinone ring;

25 R^{41} and R^{42} are independently selected from the group consisting of amidino, hydroxyamino, hydrido, hydroxy, amino, and alkyl;

Q is selected from the group consisting of hydrido, with the proviso that Z^0 is other than a covalent single bond, and the formula (II):



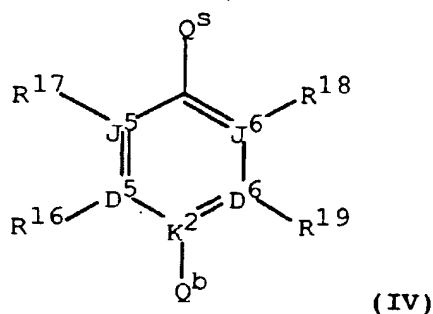
- wherein D^1 , D^2 , J^1 , J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is O, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is S, one of D^1 , D^2 , J^1 , J^2 and K^1 must be a covalent bond when two of D^1 , D^2 , J^1 , J^2 and K^1 are O and S, and no more than four of D^1 , D^2 , J^1 , J^2 and K^1 are N, with the proviso that R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

K is $(CR^{4a}R^{4b})_n$ wherein n is an integer selected from 1 through 2;

- R^{4a} and R^{4b} are independently selected from the group consisting of halo, hydrido, hydroxyalkyl, alkyl, alkoxyalkyl, alkylthioalkyl, and haloalkyl;

E^0 is E^1 , when K is $(CR^{4a}R^{4b})_n$, wherein E^1 is selected from the group consisting of a covalent single bond, C(O), C(S), C(O)N(R^7), (R^7)NC(O), S(O)₂, (R^7)NS(O)₂, and S(O)₂N(R^7);

Y^0 is formula (IV):



- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N with the proviso that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, nitro, alkoxyamino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, alkenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkylenylamino, haloalkoxyalkyl, carboalkoxy, and cyano;

- Q^b is selected from the group consisting of $NR^{20}R^{21}$, aminoalkylenyl, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy, amino, alkylamino, or dialkylamino at the same time and that no

more than one of R^{23} and R^{24} is hydroxy, amino, alkylamino, or dialkylamino at the same time;

- R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, aminoalkylenyl, amino, dialkylamino, alkylamino, and hydroxyalkyl;

- Q^s is selected from the group consisting of a single covalent bond, $(CR^{37}R^{38})_b$ wherein b is an integer selected from 1 through 4, and $(CH(R^{14}))_c-W^1-(CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 3 and W^1 is selected from the group consisting of $C(O)N(R^{14})$, $(R^{14})NC(O)$, $S(O)$, $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, and $N(R^{14})$, with the provisos that R^{14} is selected from other than halo when directly bonded to N and that $(CR^{37}R^{38})_b$ and $(CH(R^{14}))_c$ are bonded to E^0 ;

- R^{14} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;
- R^{37} and R^{38} are independently selected from the group consisting of hydrido, alkyl, and haloalkyl;

- R^{38} is optionally selected from the group consisting of aroyl and heteroaroyl;

- Y^0 is optionally Q^b-Q^{ss} wherein Q^{ss} is $(CH(R^{14}))_e-W^2-(CH(R^{15}))_h$, wherein e and h are integers independently selected from 1 through 2 and W^2 is $CR^{4a}=CR^{4b}$ with the proviso that $(CH(R^{14}))_e$ is bonded to E^0 ;

- Y^0 is optionally selected from the group consisting of Q^b-Q^{ssss} and Q^b-Q^{sssr} wherein Q^{ssss} is $(CH(R^{38}))_r-W^5$ and Q^{sssr} is $(CH(R^{38}))_r-W^6$, r is an

integer selected from 1 through 2, and W^5 and W^6 are independently selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinolinyl, 2,5-quinolinyl, 2,6-quinolinyl, 2,7-quinolinyl, 2,8-quinolinyl, 3,4-quinolinyl, 3,5-quinolinyl, 3,6-quinolinyl, 3,7-quinolinyl, 3,8-quinolinyl, 4,5-quinolinyl, 4,6-quinolinyl, 4,7-quinolinyl, 4,8-quinolinyl, 1,4-isoquinolinyl, 1,5-isoquinolinyl, 1,6-isoquinolinyl, 1,7-isoquinolinyl, 1,8-isoquinolinyl, 3,4-isoquinolinyl, 3,5-isoquinolinyl, 3,6-isoquinolinyl, 3,7-isoquinolinyl, 3,8-isoquinolinyl, 4,5-isoquinolinyl, 4,6-isoquinolinyl, 4,7-isoquinolinyl, 4,8-isoquinolinyl, 3,4-cinnolinyl, 3,5-cinnolinyl, 3,6-cinnolinyl, 3,7-cinnolinyl, 3,8-cinnolinyl, 4,5-cinnolinyl, 4,6-cinnolinyl, 4,7-cinnolinyl, and 4,8-cinnolinyl, and each carbon and hyrido containing nitrogen member of the ring of the W^5 and of the ring of the W^6 , other than the points of attachment of W^5 and W^6 , is optionally substituted with one or more of the group consisting of R^9 , R^{10} , R^{11} , and R^{12} , with the provisos that Q^b is bonded to lowest

WO 00/69832

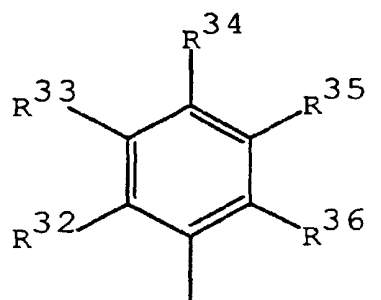
PCT/US00/09806

number substituent position of each W^5 , Q^b is bonded to highest number substituent position of each W^6 , and $(CH(R^{38}))_r$ is bonded to E^0 .

In a more preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

5 J is O;

B is the Formula:



R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the

- group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkylenedioxy, haloalkylthio, alkanoyloxy, alkoxy, hydroxy, amino, alkoxyamino, alkanoyl, haloalkanoyl, nitro, lower alkylamino, alkylthio, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, alkenyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyalkyl, alkylenylamino, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

- B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2-C8 alkyl, C3-C8 alkylenyl, C3-C8 alkenyl, C3-C8 alkynyl, and C2-C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

B is selected from the group consisting of C3-C12 cycloalkyl and C4-heterocyclyl, wherein each ring carbon may be optionally substituted with R^{33} ,

a ring carbon other than the ring carbon at the point of attachment of B to A may be optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbons and a nitrogen adjacent to the carbon at the point of attachment may be optionally substituted
 5 with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment may be substituted with R^{10} , a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment may be substituted with R^{12} , a ring carbon three atoms from the point of attachment and adjacent to the R^{10} position may be substituted with
 10 R^{11} , a ring carbon three atoms from the point of attachment and adjacent to the R^{12} position may be substituted with R^{33} , and a ring carbon four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions may be substituted with R^{34} ;

R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from the
 15 group consisting of hydrido, acetamido, haloacetamido, alkoxyamino, alkanoyl, haloalkanoyl, amidino, guanidino, alkylenedioxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl,
 20 aminoalkyl, carboalkoxy, carboxyalkyl, carboxy, carboxamido, and cyano;
 R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are optionally selected from the group consisting of heteroaryl and heterocyclyl with the proviso that R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are substituents for other than B;

A is selected from the group consisting of single covalent bond and
 25 $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is

an integer selected from 0 through 3, and W^7 is selected from the group consisting of O, S, C(O), $(R^7)NC(O)$, $(R^7)NC(S)$, and $N(R^7)$;

R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, hydroxy, halo,
5 alkyl, and haloalkyl;
 Ψ is NH;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, alkyl, cyano,
halo, haloalkyl, haloalkoxy, amino, aminoalkyl, alkylamino, amidino,
10 hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, and
alkylthio;

R^2 is Z^0-Q ;

Z^0 is selected from the group consisting of covalent single bond and
 $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 2, $(CH(R^{41}))_g-$
15 $W^0-(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0
through 3 and W^0 is selected from the group consisting of O, S, and $N(R^{41})$,
and $(CH(R^{41}))_e-W^{22}-(CH(R^{42}))_h$ wherein e and h are integers independently
selected from 0 through 1 and W^{22} is selected from the group consisting of
 $CR^{41}=CR^{42}$, 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-
20 cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-
morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-
piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl,
1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-
piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-
25 pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-

tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the proviso that Z^0 is directly bonded to the pyrimidinone ring;

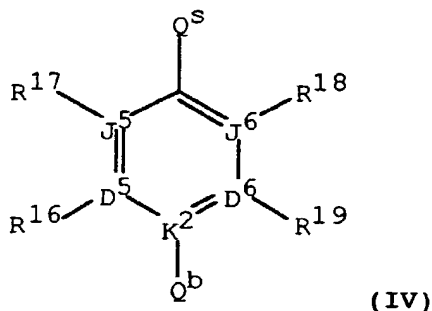
R^{41} and R^{42} are independently selected from the group consisting of hydrido, hydroxy, and amino;

- 5 Q is selected from the group consisting of hydrido, with the proviso that Z^0 is other than a covalent single bond, aryl, and heteroaryl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the
- 10 carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

- 15 K is CHR^{4a} wherein R^{4a} is selected from the group consisting of hydrido, hydroxyalkyl, alkyl, alkoxyalkyl, alkylthioalkyl, and haloalkyl;

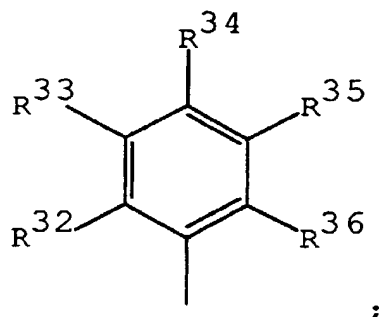
E^0 is selected from the group consisting of a covalent single bond, $C(O)N(H)$, $(H)NC(O)$, $(R^7)NS(O)_2$, and $S(O)_2N(R^7)$;

Y^0 is formula (IV):



- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N, with the provisos that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;
- R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;
- Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy, amino, alkylamino, or dialkylamino at the same time and that no more than one of R^{23} and R^{24} is hydroxy, amino, alkylamino, or dialkylamino at the same time;
- R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, amino, alkylamino and dialkylamino;
- Q^s is selected from the group consisting of a single covalent bond, $(CR^{37}R^{38})_b$ wherein b is an integer selected from 1 through 4, and

- $(\text{CH}(\text{R}^{14}))_c - \text{W}^1 - (\text{CH}(\text{R}^{15}))_d$ wherein c and d are integers independently selected from 1 through 3 and W^1 is selected from the group consisting of $\text{C}(\text{O})\text{N}(\text{R}^{14})$, $(\text{R}^{14})\text{NC}(\text{O})$, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, $\text{S}(\text{O})_2\text{N}(\text{R}^{14})$, $\text{N}(\text{R}^{14})\text{S}(\text{O})_2$, and $\text{N}(\text{R}^{14})$, with the provisos that R^{14} is selected from other than halo when
- 5 directly bonded to N and that $(\text{CR}^{37}\text{R}^{38})_b$, and $(\text{CH}(\text{R}^{14}))_c$ are bonded to E^0 ;
- R^{14} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;
- R^{37} and R^{38} are independently selected from the group consisting of hydrido, alkyl, and haloalkyl;
- 10 R^{38} is optionally selected from the group consisting of aroyl and heteroaroyl;
- Y^0 is optionally $\text{Q}^b - \text{Q}^{\text{ss}}$ wherein Q^{ss} is $(\text{CH}(\text{R}^{14}))_e - \text{W}^2 - (\text{CH}(\text{R}^{15}))_h$, wherein e and h are integers independently selected from 1 through 2 and W^2 is $\text{CR}^{4a} = \text{CH}$ with the proviso that $(\text{CH}(\text{R}^{14}))_e$ is bonded to E^0 .
- 15 In an even more preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,
- J is O;
- B is the Formula:



carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

5 R^9 , R^{11} , and R^{13} are independently selected from the group

consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

10 R^{10} and R^{12} are independently selected from the group consisting of

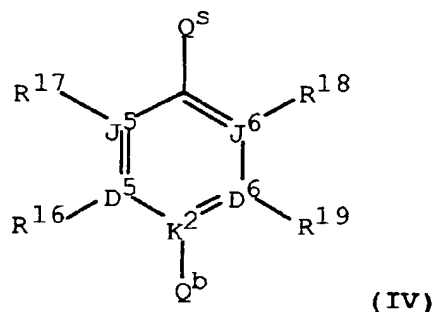
hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

15

K is CH_2 ;

E^0 is $C(O)N(H)$;

Y^0 is formula (IV):



(IV)

20 wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6

is optionally O, no more than one of D^5 , D^6 , J^5 , and J^6 is optionally S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N;

R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group

- 5 consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of

- 10 R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

- 15 R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, alkyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond,

CH_2 , and CH_2CH_2 .

- In another even more preferred embodiment of compounds of Formula
20 I or a pharmaceutically acceptable salt thereof,

J is O;

- B is optionally selected from the group consisting of hydrido, C2-C8 alkyl, C3-C8 alkenyl, C3-C8 alkynyl, and C2-C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including
25 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of $(R^7)NC(O)$ and $N(R^7)$;

R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

Ψ is NH;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

R^2 is Z^0-Q ;

Z^0 is selected from the group consisting of covalent single bond, O, S, NH, and CH_2 ;

Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the

carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

5 R^9 , R^{11} , and R^{13} are independently selected from the group

consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

10 R^{10} and R^{12} are independently selected from the group consisting of

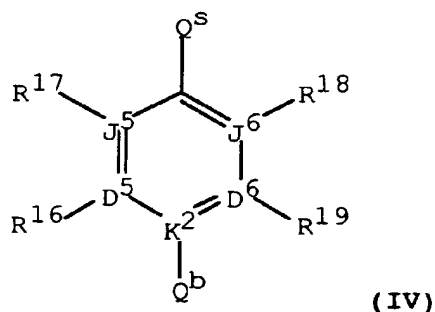
hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, alkylenylamino, carboalkoxy, carboxy, carboxyalkyl,

15 amidocarbonyl, halo, haloalkyl, and cyano;

K is CH_2 ;

E^0 is $C(O)N(H)$;

Y^0 is formula (IV):



20 wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6

- is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N, with the provisos that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkylenylamino, and cyano;
- R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;
- Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;
- R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, alkyl, and hydroxy;
- Q^s is selected from the group consisting of a single covalent bond, CH_2 , and CH_2CH_2 .

In still another even more preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,
J is O;

B is selected from the group consisting of C3-C7 cycloalkyl and C4-heterocyclyl, wherein each ring carbon may be optionally substituted with R³³, a ring carbon other than the ring carbon at the point of attachment of B to A may be optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbons and a nitrogen adjacent to the carbon at the point of attachment may be optionally substituted with R⁹ or R¹³, a ring carbon or nitrogen adjacent to the R⁹ position and two atoms from the point of attachment may be substituted with R¹⁰, a ring carbon or nitrogen adjacent to the R¹³ position and two atoms from the point of attachment may be substituted with R¹², a ring carbon three atoms from the point of attachment and adjacent to the R¹⁰ position may be substituted with R¹¹, a ring carbon three atoms from the point of attachment and adjacent to the R¹² position may be substituted with R³³, and a ring carbon four atoms from the point of attachment and adjacent to the R¹¹ and R³³ positions may be substituted with R³⁴;

R⁹, R¹¹, and R¹³ are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R¹⁰ and R¹² are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, alkylenylamino, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

- R^{33} and R^{34} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;
- A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{\pi}$ wherein π is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of $(R^7)NC(O)$ and $N(R^7)$;
- R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;
- R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;
- Ψ is NH;
- M is selected from the group consisting of N and R^1-C ;
- R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;
- R^2 is Z^0-Q ;
- Z^0 is selected from the group consisting of covalent single bond, O, S, NH, and CH_2 ;
- Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon

WO 00/69832

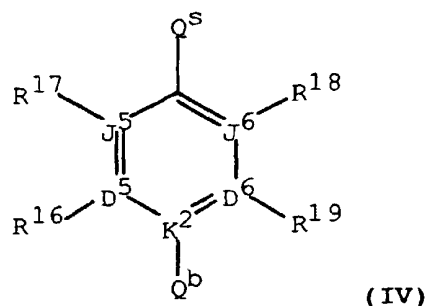
PCT/US00/09806

adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

K is CH_2 ;

5 E^0 is $C(O)N(H)$;

Y^0 is formula (IV):



wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N, with the provisos that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl,

WO 00/69832

PCT/US00/09806

alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkylenylamino, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

- 5 Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

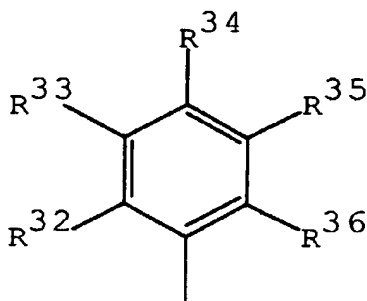
- R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group
10 consisting of hydrido, alkyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH_2 , and CH_2CH_2 .

In a most preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

- 15 J is O;

B is the Formula:



R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the

- 20 group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo,

haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is

5 an integer selected from 0 through 3, and W^7 is $N(R^7)$;

R^7 is selected from the group consisting of hydrido and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

Ψ is NH;

10 M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

15 R^2 is Z^0-Q ;

Z^0 is a covalent single bond;

Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is

20 optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

WO 00/69832

PCT/US00/09806

R^9 , R^{11} , and R^{13} are independently selected from the group

consisting of hydrido, hydroxy, amino, amidino, guanidino, lower
alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl,
monoalkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl,
5 carboxy, carboxamido, and cyano;

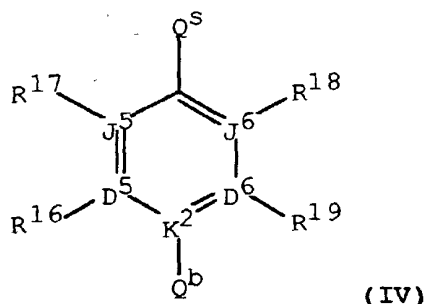
R^{10} and R^{12} are independently selected from the group consisting of

hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy,
alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino,
alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl
10 amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy,
carboxy, carboxyalkyl, carboxyamido, and cyano;

K is CH_2 ;

E^0 is $C(O)N(H)$;

Y^0 is formula (IV):



15

wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group
consisting of C, N, O, S and a covalent bond with the provisos that no more
than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6
is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6
20 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no
more than four of D^5 , D^6 , J^5 , and J^6 are N;

R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido and alkyl;

Q^s is CH_2 .

In another most preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is optionally selected from the group consisting of hydrido, C2-C8 alkyl, C3-C8 alkenyl, C3-C8 alkynyl, and C2-C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond and $(\text{CH}(\text{R}^{15}))_{\text{pa}}-(\text{W}^7)_{\text{rr}}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is $\text{N}(\text{R}^7)$;

R^7 is selected from the group consisting of hydrido and alkyl;

5 R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

Ψ is NH;

M is selected from the group consisting of N and $\text{R}^1\text{-C}$;

10 R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

R^2 is $\text{Z}^0\text{-Q}$;

Z^0 is a covalent single bond;

15 Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

20 R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl,

WO 00/69832

PCT/US00/09806

monoalkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

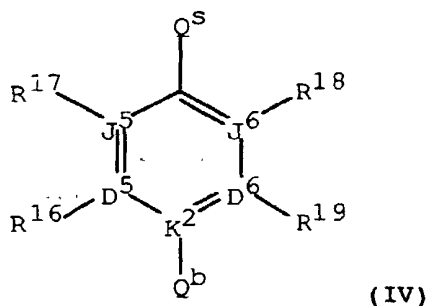
R^{10} and R^{12} are independently selected from the group consisting of

- 5 hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, carboxy, carboxyalkyl, carboxyamido, and cyano;

K is CH_2 ;

10 E^0 is $C(O)N(H)$;

Y^0 is formula (IV):



- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N, with the provisos that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- 15
- 20

R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$;

R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido and alkyl;

Q^s is CH_2 .

In still another most preferred embodiment of compounds of Formula I or a pharmaceutically acceptable salt thereof,

J is O;

B is selected from the group consisting of C3-C7 cycloalkyl and C4-heterocyclyl, wherein each ring carbon may be optionally substituted with R^{33} , a ring carbon other than the ring carbon at the point of attachment of B to A may be optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbons and nitrogens adjacent to the carbon at the point of attachment may be optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment may be substituted with R^{10} , a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment may be substituted with R^{12} , a ring carbon three atoms from the point of attachment and adjacent to the R^{10} position may be substituted with

R^{11} , a ring carbon three atoms from the point of attachment and adjacent to the R^{12} position may be substituted with R^{33} , and a ring carbon four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions may be substituted with R^{34} ;

- 5 R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;
- 10 R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, carboxy, carboxyalkyl, carboxyamido, and cyano;
- 15 R^{33} and R^{34} are independently selected from the group consisting of hydrido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, and cyano;

- 20 R^{33} is optionally Q^b ;
- A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is $N(R^7)$;
- 25 R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;
- R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

Ψ is NH;

M is selected from the group consisting of N and R^1 -C;

R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

R^2 is Z^0 -Q;

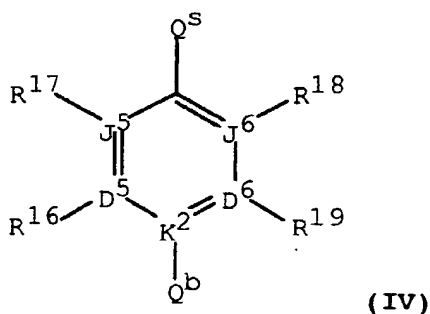
Z^0 is a covalent single bond;

Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

K is CH_2 ;

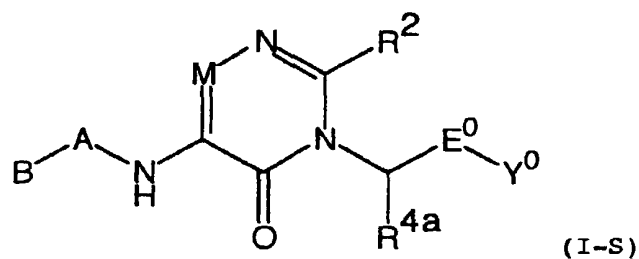
E^0 is $C(O)N(H)$;

Y^0 is formula (IV):



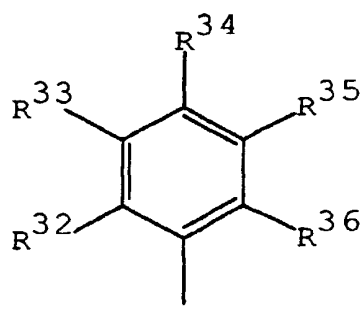
- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N, with the provisos that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;
- 10 R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkylenylamino, and cyano;
- 15 R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;
- Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$;
- R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group
- 20 consisting of hydrido and alkyl;
- Q^s is CH_2 .

In a preferred specific embodiment of Formula I, compounds have the Formula I-S:



or a pharmaceutically acceptable salt thereof, wherein;

B is the Formula:



5 R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, isopropyl, propyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, nitro, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidulosulfonyl, N,N-dimethylamidulosulfonyl, acetyl, propanoyl, trifluoroacetyl, pentafluoropropanoyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, 2,2,2-trifluoro-1-trifluoromethyl-1-hydroxyethyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b ;

20 B is selected from the group consisting of hydrido, trimethylsilyl, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butenyl, 3-butenyl,

- 2-butenyl, sec-butyl, *tert*-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentyl, 1-methyl-2-butenyl, 1-methyl-3-butenyl, 1-methyl-2-butenyl, 3-pentyl, 1-ethyl-2-propenyl, 2-methylbutyl, 2-methyl-2-butenyl, 2-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methylbutyl, 3-methyl-2-butenyl, 3-methyl-3-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-4-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 1-propyl-2-propenyl, 1-ethyl-2-butenyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl-4-hexenyl, 1-methyl-5-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-4-pentenyl, 1-butyl-2-propenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 1-octyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 2-octynyl, 3-octynyl, 4-octynyl, 5-octynyl, 6-octynyl, 2-octyl, 1-methyl-2-heptenyl, 1-methyl-3-heptenyl, 1-methyl-4-heptenyl, 1-methyl-5-heptenyl, 1-methyl-6-heptenyl, 1-methyl-2-heptynyl, 1-methyl-3-heptynyl, 1-methyl-4-heptenyl, 1-methyl-5-heptenyl, 1-methyl-6-heptenyl, 1-methyl-2-heptenyl, 1-methyl-3-heptynyl, 1-methyl-4-heptynyl, 1-methyl-5-heptynyl, 3-octyl, 1-ethyl-2-hexenyl, 1-ethyl-3-hexenyl, 1-ethyl-4-hexenyl, 1-ethyl-2-hexynyl, 1-ethyl-3-hexynyl, 1-ethyl-4-hexynyl, 1-ethyl-5-hexenyl, 1-pentyl-2-propenyl, 4-octyl, 1-propyl-2-pentenyl, 1-propyl-3-pentenyl, 1-propyl-4-pentenyl, 1-butyl-2-butenyl, 1-propyl-2-pentynyl, 1-propyl-3-pentynyl, 1-butyl-2-butenyl, 1-butyl-3-butenyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R³², R³³, R³⁴, R³⁵, and R³⁶;

B is optionally selected from the group consisting of cyclopropyl, cyclobutyl, oxetan-2-yl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, thiaetan-2-yl, thiaetan-3-yl, cyclopentyl, cyclohexyl, adamantyl, norbornyl, 3-trifluoromethylnorbornyl, bicyclo[3.1.0]hexan-6-yl, cycloheptyl, and

cyclooctyl, wherein each ring carbon is optionally substituted with R^{33} , ring carbons or a nitrogen adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13} , a ring carbon or a nitrogen adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10} , and a ring carbon or a nitrogen adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12} ;

R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, isopropyl, propyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, nitro, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, acetyl, propanoyl, trifluoroacetyl, pentafluoropropanoyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, 2,2,2-trifluoro-1-trifluoromethyl-1-hydroxyethyl, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

A is selected from the group consisting of single covalent bond, O, S, NH, N(CH₃), N(OH), C(O), CH₂, CH₃CH, CF₃CH, NHC(O), N(CH₃)C(O), C(O)NH, C(O)N(CH₃), CF₃CC(O), C(O)CCH₃, C(O)CCF₃, CH₂C(O), (O)CCH₂, CH₂CH₂, CH₂CH₂CH₂, CH₃CHCH₂, CF₃CHCH₂, CH₃CC(O)CH₂, CF₃CC(O)CH₂, CH₂C(O)CCH₃, CH₂C(O)CCF₃, CH₂CH₂C(O), and CH₂(O)CCH₂;

A is optionally selected from the group consisting of $\text{CH}_2\text{N}(\text{CH}_3)$, $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)$, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)$, and $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)$ with the proviso that B is hydrido;

M is selected from the group consisting of N and $\text{R}^1\text{-C}$;

- 5 R^1 is selected from the group consisting of hydrido, hydroxy, amino, thiol, amidino, hydroxyamino, aminomethyl, 1-aminoethyl, 2-aminoethyl, methylamino, dimethylamino, cyano, methyl, ethyl, isopropyl, propyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, methoxy, ethoxy, propoxy, hydroxymethyl, 1-
10 hydroxyethyl, 2-hydroxyethyl, methoxyamino, ethoxyamino, methylthio, ethylthio, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, and bromo;

R^2 is $\text{Z}^0\text{-Q}$;

Z^0 is selected from the group consisting of covalent single bond, O, S,

- 15 NH , CH_2 , CH_2CH_2 , $\text{CH}(\text{OH})$, $\text{CH}(\text{NH}_2)$, $\text{CH}_2\text{CH}(\text{OH})$, CH_2CHNH_2 , $\text{CH}(\text{OH})\text{CH}_2$, and $\text{CH}(\text{NH}_2)\text{CH}_2$;

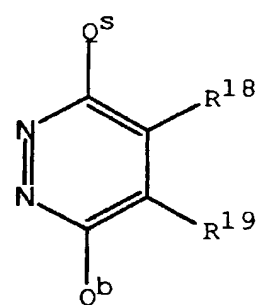
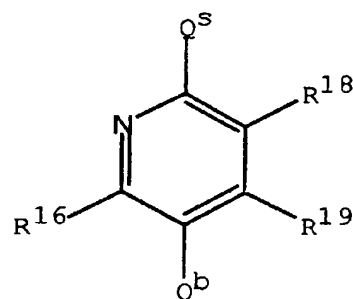
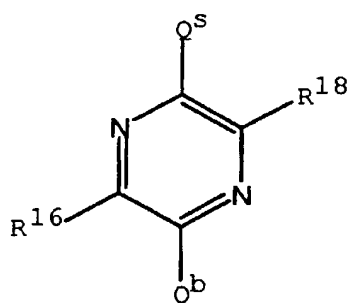
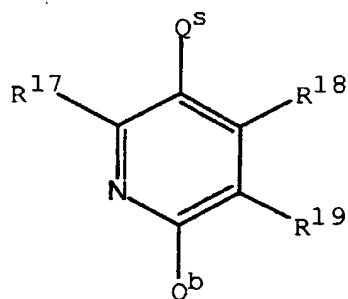
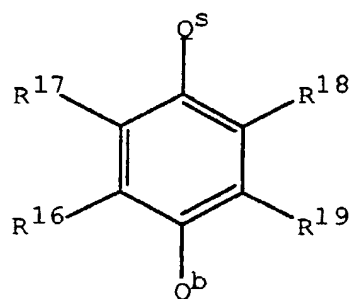
- Q is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,4-oxadiazol-
20 3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-3-yl, 1,3,4-oxadiazol-5-yl, 3-isothiazolyl, 5-isothiazolyl, 2-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, 1,2,3-triazin-4-yl, and 1,2,3-triazin-
25 5-yl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at

the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

K is CHR^{4a} wherein R^{4a} is selected from the group consisting of methyl, ethyl, propyl, isopropyl, hydroxymethyl, 1-hydroxyethyl, methoxymethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoromethyl, methylthiomethyl, and hydrido;

E^0 is a covalent single bond, $C(O)N(H)$, $(H)NC(O)$, and $S(O)_2N(H)$;

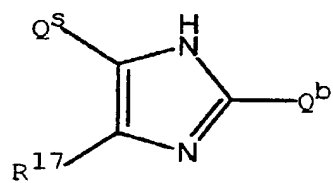
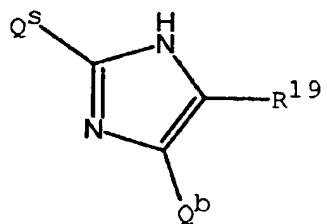
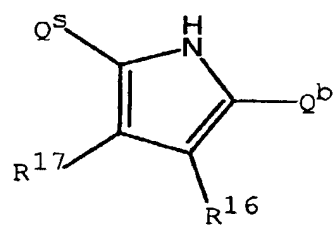
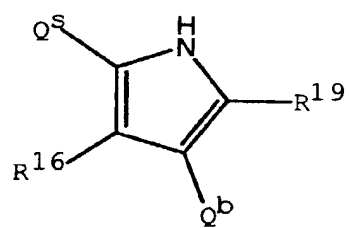
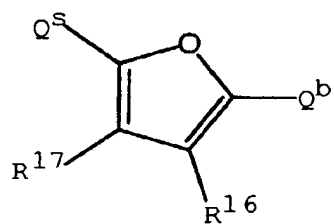
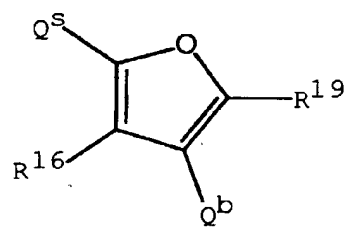
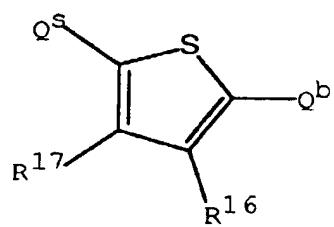
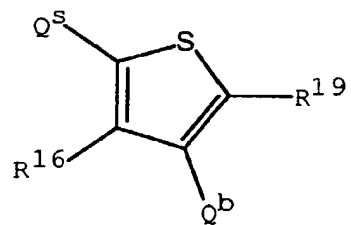
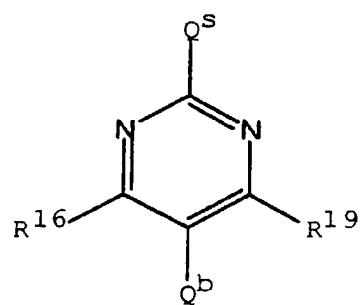
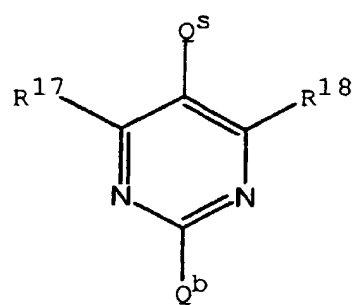
Y^0 is selected from the group of formulas consisting of:

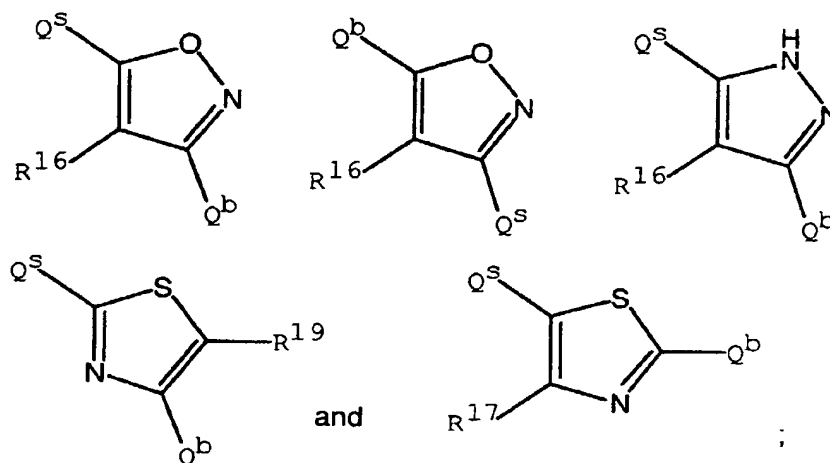


10

WO 00/69832

PCT/US00/09806





R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group

- consisting of hydrido, methyl, ethyl, isopropyl, propyl, amidino, guanidino,
 5 carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino,
 methoxyamino, ethoxyamino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-
 N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio,
 isopropylthio, trifluoromethylthio, methylsulfinyl, ethylsulfinyl,
 methylsulfonyl, ethylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-
 10 trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-
 tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-
 methylamidosulfonyl, N,N-dimethylamidosulfonyl, acetyl, propanoyl,
 trifluoroacetyl, pentafluoropropanoyl, hydroxymethyl, 1-hydroxyethyl, 2-
 hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano;

- 15 R^{16} and R^{19} are optionally Q^b with the proviso that no more than one
 of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein
 Q^{be} is hydrido, $C(NR^{25})NR^{23}R^{24}$ and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with
 the proviso that no more than one of R^{20} and R^{21} is hydroxy, N-
 20 methylamino, and N,N-dimethylamino at the same time and that no more than

WO 00/69832

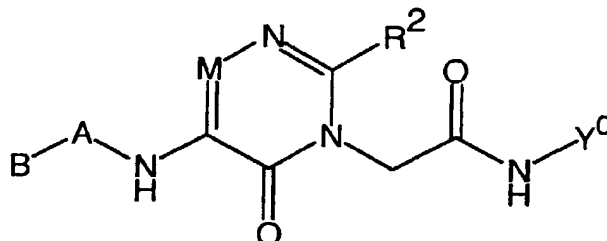
PCT/US00/09806

one of R^{23} and R^{24} is hydroxy, N-methylamino, and N,N-dimethylamino at the same time;

R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, hydroxy, 2-aminoethyl, 2-(N-methylamino)ethyl, and 2-(N,N-dimethylamino)ethyl;

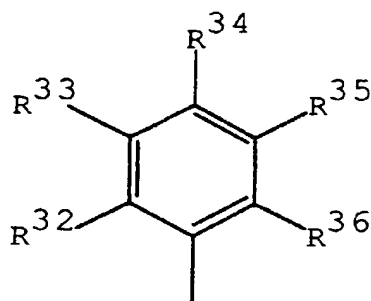
Q^s is selected from the group consisting of a single covalent bond, CH_2 , CH_2CH_2 , CH_3CH , CF_3CH , CH_3CHCH_2 , CF_3CHCH_2 , $CH_2(CH_3)CH$, $CH=CH$, $CF=CH$, $C(CH_3)=CH$, $CH=CHCH_2$, $CF=CHCH_2$, $C(CH_3)=CHCH_2$, $CH_2CH=CH$, $CH_2CF=CH$, $CH_2C(CH_3)=CH$, $CH_2CH=CHCH_2$, $CH_2CF=CHCH_2$, $CH_2C(CH_3)=CHCH_2$, $CH_2CH=CHCH_2CH_2$, $CH_2CF=CHCH_2CH_2$, and $CH_2C(CH_3)=CHCH_2CH_2$.

In a more preferred specific embodiment of Formula I, compounds have the Formula I-MPS wherein B is an aromatic:



15

(I-MPS wherein B is aromatic)
or a pharmaceutically acceptable salt thereof, wherein;
B is the Formula:



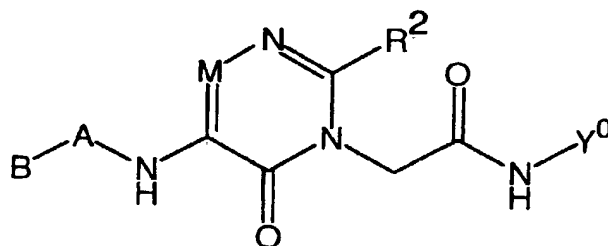
- R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamid sulfonyl, N,N-dimethylamid sulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b ;

- A is selected from the group consisting of single covalent bond, NH, $N(CH_3)$, $N(OH)$, CH_2 , CH_3CH , CF_3CH , $NHC(O)$, $N(CH_3)C(O)$, $C(O)NH$, $C(O)N(CH_3)$, CH_2CH_2 , $CH_2CH_2CH_2$, CH_3CHCH_2 , and CF_3CHCH_2 ;

- Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;
- R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

Q^5 is selected from the group consisting of a single covalent bond, CH_2 , and CH_2CH_2 .

In another more preferred specific embodiment of Formula I, compounds have the Formula I-MPS wherein B is a non-cyclic substituent:



(I-MPS)

wherein B is a non-cyclic substituent)
or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butenyl, 3-butenyl, 2-butylnyl, sec-butyl, *tert*-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentylnyl, 1-methyl-2-butenyl, 1-methyl-3-butenyl, 1-methyl-2-butylnyl, 3-pentyl, 1-ethyl-2-propenyl, 2-methylbutyl, 2-methyl-2-butenyl, 2-methyl-3-butenyl, 2-methyl-3-butylnyl, 3-methylbutyl, 3-methyl-2-butenyl, 3-methyl-3-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-4-pentenyl, 1-methyl-2-pentylnyl, 1-methyl-3-pentylnyl, 3-hexyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 1-propyl-2-propenyl, 1-ethyl-2-butylnyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl-4-hexenyl, 1-methyl-5-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-4-pentenyl, 1-butyl-2-propenyl, 1-ethyl-2-pentylnyl, 1-ethyl-3-pentylnyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamid sulfonyl, N,N-dimethylamid sulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond, NH, N(CH₃), N(OH), CH₂, CH₃CH, CF₃CH, NHC(O), N(CH₃)C(O), C(O)NH, C(O)N(CH₃), CH₂CH₂, CH₂CH₂CH₂, CH₃CHCH₂, and CF₃CHCH₂;

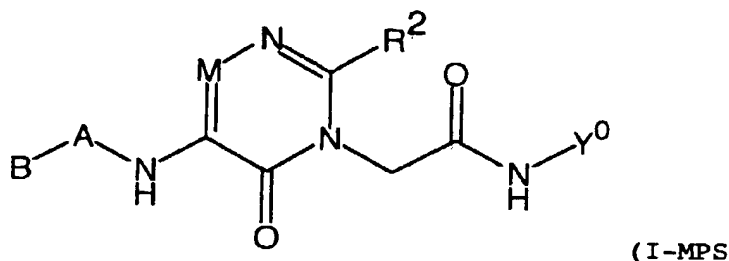
A is optionally selected from the group consisting of CH₂N(CH₃), CH₂N(CH₂CH₃), CH₂CH₂N(CH₃), and CH₂CH₂N(CH₂CH₃) with the proviso that B is hydrido;

Q^b is selected from the group consisting of NR²⁰R²¹, Q^{be} , wherein Q^{be} is hydrido, C(NR²⁵)NR²³R²⁴, and N(R²⁶)C(NR²⁵)N(R²³)(R²⁴), with the provisos that no more than one of R²⁰ and R²¹ is hydroxy at the same time and that no more than one of R²³ and R²⁴ is hydroxy at the same time;

R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH₂, and CH₂CH₂.

In still another more preferred specific embodiment of Formula I, compounds have the Formula I-MPS wherein B is a non-aromatic cyclic substituent:



- 5 wherein B is a non-aromatic cyclic substituent) or a pharmaceutically acceptable salt thereof, wherein;

- B is optionally selected from the group consisting of cyclopropyl, cyclobutyl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, thiaetan-3-yl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[3.1.0]hexan-6-yl, and
- 10 cycloheptyl, wherein each ring carbon is optionally substituted with R^{33} , ring carbons or a nitrogen adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment is optionally
- substituted with R^{10} , and a ring carbon or nitrogen adjacent to the R^{13}
- 15 position and two atoms from the point of attachment is optionally substituted with R^{12} ;

- A is selected from the group consisting of single covalent bond, NH, $N(CH_3)$, $N(OH)$, CH_2 , CH_3CH , CF_3CH , $NHC(O)$, $N(CH_3)C(O)$, $C(O)NH$, $C(O)N(CH_3)$, CH_2CH_2 , $CH_2CH_2CH_2$, CH_3CHCH_2 , and
- 20 CF_3CHCH_2 ;

R^{33} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio,

WO 00/69832

PCT/US00/09806

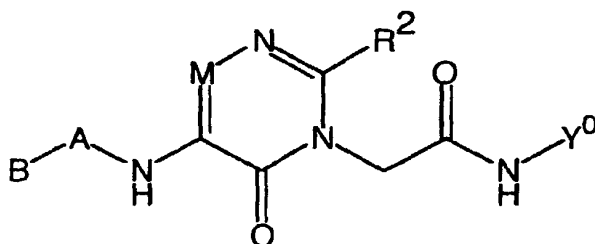
- isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamid sulfonyl, N,N-dimethylamid sulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 5 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b ;

- Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} 10 and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

- Q^s is selected from the group consisting of a single covalent bond, 15 CH_2 , and CH_2CH_2 .

The more preferred specific embodiment (I-MPS) compounds of the present invention having the Formula:



- or a pharmaceutically acceptable salt thereof, have common structural units, 20 wherein;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, 1-aminoethyl, methylamino, dimethylamino, cyano, methyl, ethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-

trifluoroethyl, methoxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxyamino, methylthio, ethylthio, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, and bromo;

R^2 is Z^0-Q ;

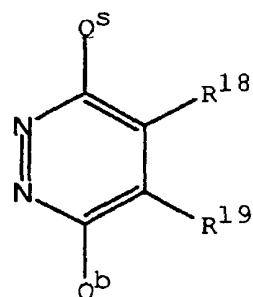
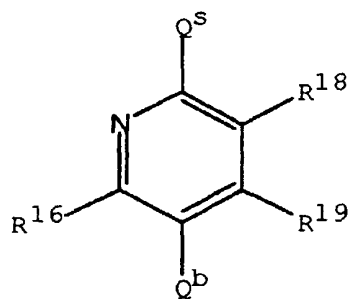
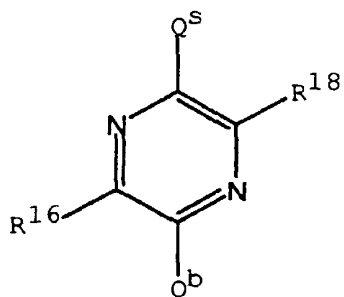
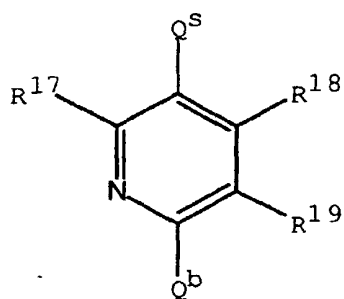
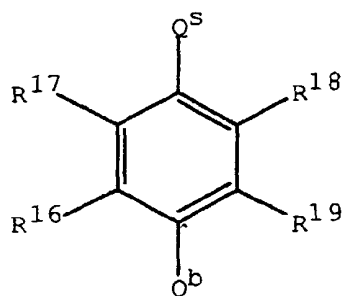
5 Z^0 is selected from the group consisting of covalent single bond, O, S, NH, and CH_2 ;

Q is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

10 R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidossulfonyl, N,N-dimethylamidossulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

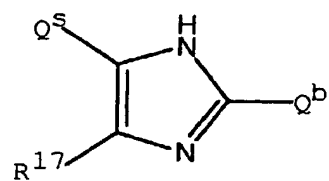
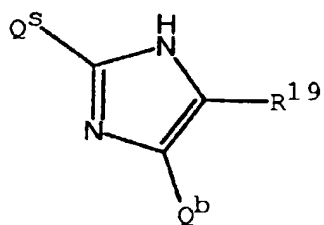
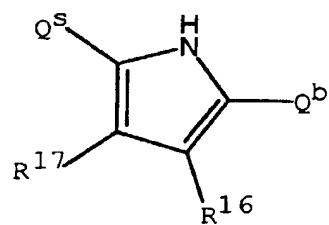
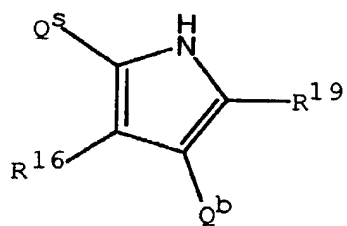
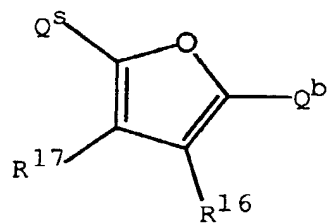
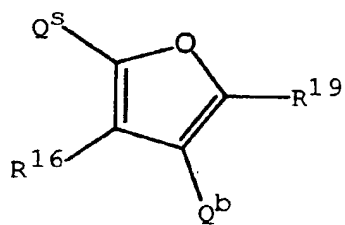
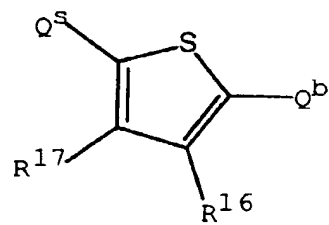
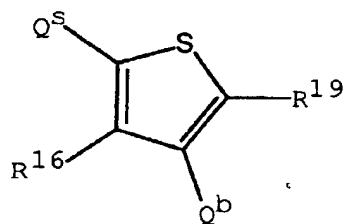
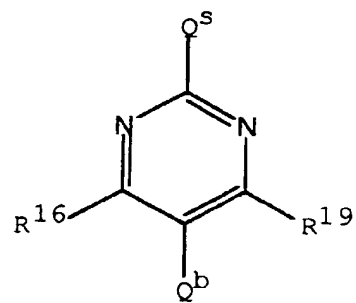
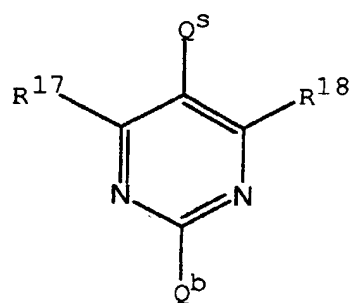
- R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methanesulfonamido, amidosulfonyl, N-methylamidulosulfonyl, N,N-dimethylamidulosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group of formulas consisting of:



WO 00/69832

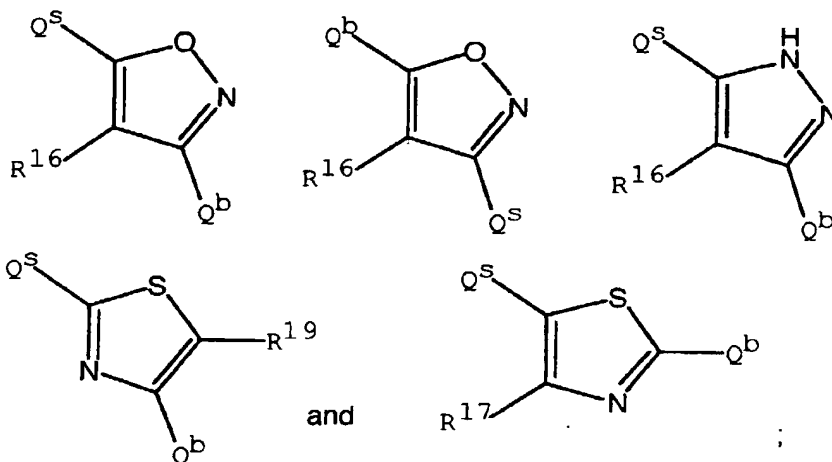
PCT/US00/09806



5

WO 00/69832

PCT/US00/09806



R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group

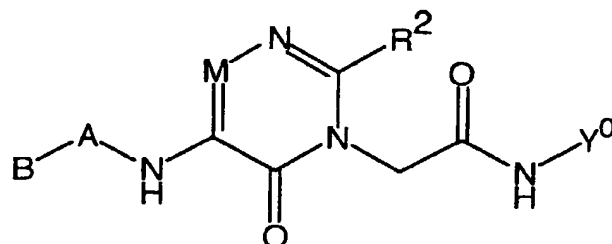
- 5 consisting of hydrido, methyl, ethyl, isopropyl, propyl, carboxy, amidino, guanidino, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo,
- 10 amidosulfonyl, N-methylamidossulfonyl, N,N-dimethylamidossulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano;

- R^{16} and R^{19} are optionally Q^b with the proviso that no more than one
- 15 of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} .

In a most preferred specific embodiment of Formula I, compounds have the Formula I-EMPS wherein B is an aromatic:

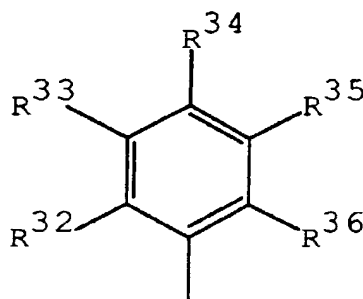
WO 00/69832

PCT/US00/09806



(I-EMPS wherein B is aromatic)
or a pharmaceutically acceptable salt thereof, wherein;

B is the Formula:



5

R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the

group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, amidocarbonyl, carboxy, cyano, and Q^b ;

10

A is selected from the group consisting of single covalent bond, NH, N(CH₃), CH₂, CH₃CH, and CH₂CH₂;

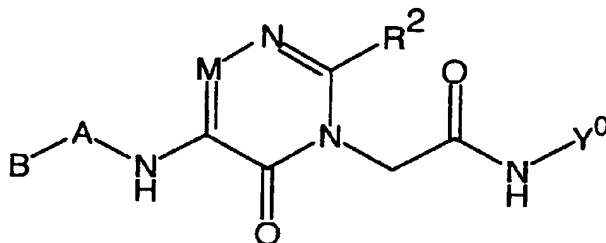
Q^b is selected from the group consisting of NR²⁰R²¹ and

15 C(NR²⁵)NR²³R²⁴, with the proviso that said Q^b group is bonded directly to a carbon atom;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, methyl, and ethyl;

Q^s is CH_2 .

In another most preferred specific embodiment of Formula I, compounds have the Formula I-EMPS wherein B is a non-cyclic substituent:



(I-EMPS)

- 5 wherein B is a non-cyclic substituent)
or a pharmaceutically acceptable salt thereof, wherein;
- B is selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butenyl, 2-butylnyl, sec-butyl, *tert*-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 2-
10 pentynyl, 3-pentynyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 2-methyl-2-butenyl, 3-methylbutyl, 3-methyl-2-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl-4-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;
20 R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the
25 group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro,

WO 00/69832

PCT/US00/09806

chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, amidocarbonyl, carboxy, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond, NH, N(CH₃), CH₂, CH₃CH, and CH₂CH₂;

- 5 A is optionally selected from the group consisting of CH₂N(CH₃), CH₂N(CH₂CH₃), CH₂CH₂N(CH₃), and CH₂CH₂N(CH₂CH₃) with the proviso that B is hydrido;

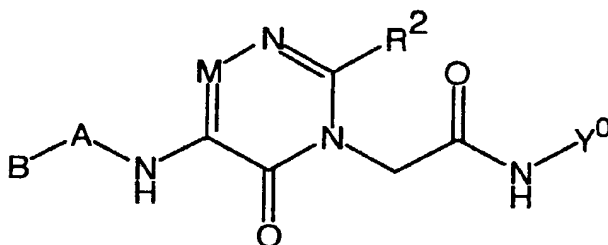
Q^b is selected from the group consisting of NR²⁰R²¹, C(NR²⁵)NR²³R²⁴, and N(R²⁶)C(NR²⁵)N(R²³)(R²⁴), with the proviso that

- 10 said Q^b group is bonded directly to a carbon atom;

R²⁰, R²¹, R²³, R²⁴, R²⁵, and R²⁶ are independently selected from the group consisting of hydrido, methyl, and ethyl;

Q^s is CH₂.

- 15 In still another most preferred specific embodiment of Formula I, compounds have the Formula I-EMPS wherein B is a non-aromatic cyclic substituent:



- (I-EMPS wherein B is a non-aromatic cyclic substituent)
20 or a pharmaceutically acceptable salt thereof, wherein;

B is optionally selected from the group consisting of cyclopropyl, cyclobutyl, oxetan-3-yl, azetidin-3-yl, thiaetan-3-yl, cyclopentyl, and cyclohexyl, wherein each ring carbon is optionally substituted with R³³, ring

WO 00/69832

PCT/US00/09806

carbons or a nitrogen adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10} , and a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12} ;

R^{33} are independently selected from the group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, carboxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidulosulfonyl, hydroxymethyl, amidocarbonyl, cyano, and Q^b ;

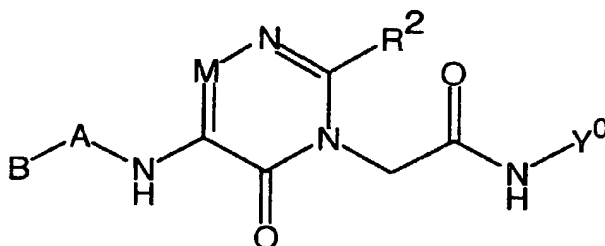
A is selected from the group consisting of single covalent bond, NH, N(CH₃), CH₂, CH₃CH, and CH₂CH₂;

Q^b is selected from the group consisting of $NR^{20}R^{21}$ and $C(NR^{25})NR^{23}R^{24}$, with the proviso that said Q^b group is bonded directly to a carbon atom;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, methyl, and ethyl;

Q^s is CH₂.

The most preferred specific embodiment (I-EMPS) compounds of the present invention having the Formula:



or a pharmaceutically acceptable salt thereof, have common structural units, wherein;

M is selected from the group consisting of N and R¹-C;

5 R¹ is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, methylamino, cyano, methyl, trifluoromethyl, methoxy, hydroxymethyl, methoxyamino, methylthio, trifluoromethoxy, fluoro, and chloro;

R² is Z⁰-Q;

Z⁰ is a covalent single bond;

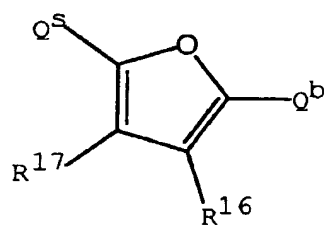
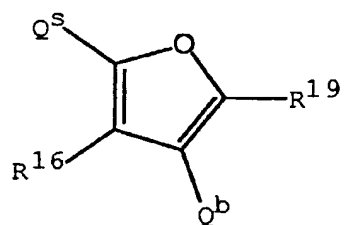
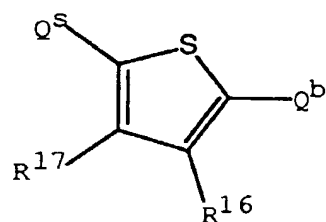
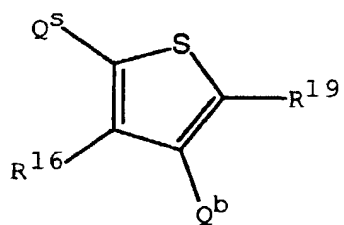
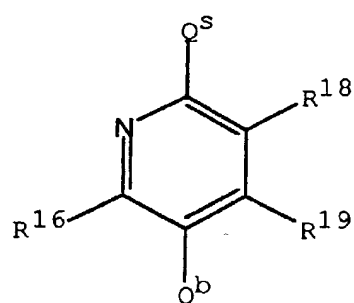
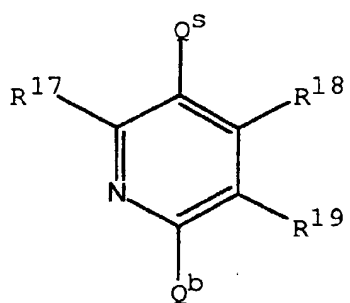
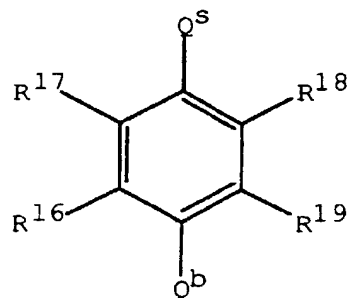
10 Q is selected from the group consisting of phenyl, 2-thienyl, 2-furyl, 2-pyrrolyl, 2-imidazolyl, 2-thiazolyl, 3-isoxazolyl, 2-pyridyl, and 3-pyridyl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R⁹, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R¹³, a carbon adjacent to R⁹ and two
15 atoms from the carbon at the point of attachment is optionally substituted by R¹⁰, a carbon adjacent to R¹³ and two atoms from the carbon at the point of attachment is optionally substituted by R¹², and any carbon adjacent to both R¹⁰ and R¹² is optionally substituted by R¹¹;

R⁹, R¹¹, and R¹³ are independently selected from the group consisting
20 of hydrido, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, methylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, hydroxymethyl, 1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, carboxy, and cyano;

25 R¹⁰ and R¹² are independently selected from the group consisting of hydrido, amidino, amidocarbonyl, N-methylamidocarbonyl, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, carboxy, carboxymethyl, amino, acetamido, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoroacetamido, aminomethyl, N-

methylamino, dimethylamino, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, methoxycarbonyl, fluoro, chloro, bromo, and cyano;

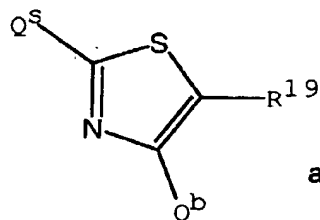
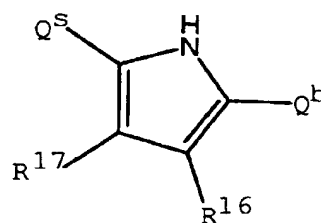
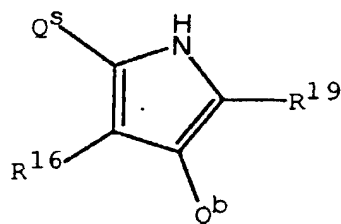
Y^0 is selected from the group of formulas consisting of:



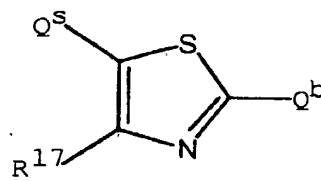
5

WO 00/69832

PCT/US00/09806



and



- 5 R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, amidino, guanidino, methoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethylthio, methylsulfinyl, methylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 10 trifluoromethoxy, fluoro, chloro, amidosulfonyl, N-methylamid sulfonyl, hydroxymethyl, carboxy, and cyano.

- The compounds of this invention can be used in anticoagulant therapy for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular disease. The compounds of this invention 15 can be used to inhibit serine protease associated with the coagulation cascade and factors II, VII, VIII, IX, X, XI, or XII. The compounds of the invention can inhibit the formation of blood platelet aggregates, inhibit the formation of fibrin, inhibit thrombus formation, and inhibiting embolus formation in a mammal, in blood, in blood products, and in mammalian organs. The 20 compounds also can be used for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels in a mammal. The compounds 25 can also be used in prophylactic treatment of subjects who are at risk of

developing such disorders. The compounds can be used to lower the risk of atherosclerosis. The compounds of Formula (I) would also be useful in prevention of cerebral vascular accident (CVA) or stroke.

Besides being useful for human treatment, these compounds are also
5 useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

In yet another embodiment of the present invention, the novel
compounds are selected from the compounds set forth in Examples 1 through
10 Example 19 and Tables 1.

The use of generic terms in the description of the compounds are herein defined for clarity.

Standard single letter elemental symbols are used to represent specific types of atoms unless otherwise defined. The symbol "C" represents a carbon atom.
15 The symbol "O" represents an oxygen atom. The symbol "N" represents a nitrogen atom. The symbol "P" represents a phosphorus atom. The symbol "S" represents a sulfur atom. The symbol "H" represents a hydrido atom. Double letter elemental symbols are used as defined for the elements of the periodical table (i.e., Cl represents chlorine, Se represents selenium, etc.).

20 As utilized herein, the term "alkyl", either alone or within other terms such as "haloalkyl" and "alkylthio", means an acyclic alkyl radical containing from 1 to about 10, preferably from 3 to about 8 carbon atoms and more preferably 3 to about 6 carbon atoms. Said alkyl radicals may be optionally substituted with groups as defined below. Examples of such radicals include methyl, ethyl,
25 chloroethyl, hydroxyethyl, n-propyl, oxopropyl, isopropyl, n-butyl, cyanobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, aminopentyl, iso-amyl, hexyl, octyl and the like.

The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains at least one double bond. Such alkenyl radicals contain
30 from about 2 to about 10 carbon atoms, preferably from about 3 to about 8 carbon atoms and more preferably 3 to about 6 carbon atoms. Said alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl,
35 hepten-1-yl, and octen-1-yl, and the like.

The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 3 to about 8 carbon atoms and more preferably having 3 to about 6 carbon atoms. Said
5 alkynyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

10 The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a "hydroxyl" radical, one hydrido radical may be attached to a carbon atom to form a "methine" radical -CH= , or two hydrido radicals may be attached to a carbon atom to form a "methylene" ($\text{-CH}_2\text{-}$) radical.

15 The term "carbon" radical denotes a carbon atom without any covalent bonds and capable of forming four covalent bonds.

The term "cyano" radical denotes a carbon radical having three of four covalent bonds shared by a nitrogen atom.

20 The term "hydroxyalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with a hydroxyl as defined above. Specifically embraced are monohydroxyalkyl, dihydroxyalkyl and polyhydroxyalkyl radicals.

25 The term "alkanoyl" embraces radicals wherein one or more of the terminal alkyl carbon atoms are substituted with one or more carbonyl radicals as defined below. Specifically embraced are monocarbonylalkyl and dicarbonylalkyl radicals. Examples of monocarbonylalkyl radicals include formyl, acetyl, and pentanoyl. Examples of dicarbonylalkyl radicals include oxalyl, malonyl, and succinyl.

30 The term "alkylene" radical denotes linear or branched radicals having from 1 to about 10 carbon atoms and having attachment points for two or more covalent bonds. Examples of such radicals are methylene, ethylene, methylethylene, and isopropylidene.

The term "alkenylene" radical denotes linear or branched radicals having from 2 to about 10 carbon atoms, at least one double bond, and having

attachment points for two or more covalent bonds. Examples of such radicals are 1,1-vinylidene ($\text{CH}_2=\text{C}$), 1,2-vinylidene ($-\text{CH}=\text{CH}-$), and 1,4-butadienyl ($-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$).

5 The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a
10 fluoro atom within the radical. Dihaloradicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkyl radicals are "lower haloalkyl" radicals having one to about six carbon atoms. Examples of such haloalkyl
15 radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trifluoroethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

The term "hydroxyhaloalkyl" embraces radicals wherein any one or
20 more of the haloalkyl carbon atoms is substituted with hydroxy as defined above. Examples of "hydroxyhaloalkyl" radicals include hexafluorohydroxypropyl.

The term "haloalkylene radical" denotes alkylene radicals wherein any one or more of the alkylene carbon atoms is substituted with halo as defined
25 above. Dihaloradicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkylene radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkylene radicals are "lower haloalkylene" radicals having one to about six carbon atoms. Examples of "haloalkylene"
30 radicals include difluoromethylene, tetrafluoroethylene, tetrachloroethylene, alkyl substituted monofluoromethylene, and aryl substituted trifluoromethylene.

The term "haloalkenyl" denotes linear or branched radicals having from 1 to about 10 carbon atoms and having one or more double bonds wherein any
35 one or more of the alkenyl carbon atoms is substituted with halo as defined

above. Dihaloalkenyl radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkenyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

5 The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxy
10 radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy, isopropoxy and *tert*-butoxy alkyls. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" and "haloalkoxyalkyl" radicals. Examples of such haloalkoxy radicals include
15 fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and fluoropropoxy. Examples of such haloalkoxyalkyl radicals include fluoromethoxymethyl, chloromethoxyethyl, trifluoromethoxymethyl, difluoromethoxyethyl, and trifluoroethoxymethyl.

20 The terms "alkenyloxy" and "alkenyloxyalkyl" embrace linear or branched oxy-containing radicals each having alkenyl portions of two to about ten carbon atoms, such as ethenyloxy or propenyloxy radical. The term "alkenyloxyalkyl" also embraces alkenyl radicals having one or more
25 alkenyloxy radicals attached to the alkyl radical, that is, to form monoalkenyloxyalkyl and dialkenyloxyalkyl radicals. More preferred alkenyloxy radicals are "lower alkenyloxy" radicals having two to six carbon atoms. Examples of such radicals include ethenyloxy, propenyloxy, butenyloxy, and isopropenyloxy alkyls. The "alkenyloxy" radicals may be
30 further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkenyloxy" radicals. Examples of such radicals include trifluoroethenyloxy, fluoroethenyloxy, difluoroethenyloxy, and fluoropropenyloxy.

 The term "haloalkoxyalkyl" also embraces alkyl radicals having one or more haloalkoxy radicals attached to the alkyl radical, that is, to form
35 monohaloalkoxyalkyl and dihaloalkoxyalkyl radicals. The term

"haloalkenyloxy" also embraces oxygen radicals having one or more haloalkenyloxy radicals attached to the oxygen radical, that is, to form monohaloalkenyloxy and dihaloalkenyloxy radicals. The term "haloalkenyloxyalkyl" also embraces alkyl radicals having one or more
5 haloalkenyloxy radicals attached to the alkyl radical, that is, to form monohaloalkenyloxyalkyl and dihaloalkenyloxyalkyl radicals.

The term "alkylenedioxy" radicals denotes alkylene radicals having at least two oxygens bonded to a single alkylene group. Examples of "alkylenedioxy" radicals include methylenedioxy, ethylenedioxy,
10 alkylsubstituted methylenedioxy, and arylsubstituted methylenedioxy. The term "haloalkylenedioxy" radicals denotes haloalkylene radicals having at least two oxy groups bonded to a single haloalkyl group. Examples of "haloalkylenedioxy" radicals include difluoromethylenedioxy, tetrafluoroethylenedioxy, tetrachloroethylenedioxy, alkylsubstituted
15 monofluoromethylenedioxy, and arylsubstituted monofluoromethylenedioxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused. The term "fused" means that a second ring is present (ie, attached or formed) by having two adjacent atoms in
20 common (ie, shared) with the first ring. The term "fused" is equivalent to the term "condensed". The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

The term "perhaloaryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl wherein the aryl radical is substituted with 3 or more halo radicals as defined below.
25

The term "heterocyclyl" embraces saturated and partially saturated heteroatom-containing ring-shaped radicals having from 4 through 15 ring members, herein referred to as "C4-C15 heterocyclyl" selected from carbon, nitrogen, sulfur and oxygen, wherein at least one ring atom is a heteroatom.
30 Heterocyclyl radicals may contain one, two or three rings wherein such rings may be attached in a pendant manner or may be fused. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group
35 containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl,

etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Non-limiting examples of
 5 heterocyclic radicals include 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, and the like.

The term "heteroaryl" embraces fully unsaturated heteroatom-containing ring-shaped aromatic radicals having from 5 through 15 ring members selected
 10 from carbon, nitrogen, sulfur and oxygen, wherein at least one ring atom is a heteroatom. Heteroaryl radicals may contain one, two or three rings wherein such rings may be attached in a pendant manner or may be fused. Examples of "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl,
 15 imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl,
 20 isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered
 25 heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered
 30 heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces
 35 radicals where heterocyclic radicals are fused with aryl radicals. Examples of

such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl" group may have 1 to 3 substituents as defined below. Preferred heterocyclic radicals include five to twelve membered fused or unfused radicals. Non-limiting examples of heteroaryl radicals include

5 pyrrolyl, pyridinyl, pyridyloxy, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrazolyl, 2-imidazoliny, imidazolidinyl, 2-pyrazoliny, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl,

10 benzimidazolyl, quinolinyl, tetraazolyl, and the like.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. "Alkylsulfonylalkyl", embraces alkylsulfonyl radicals attached to an

15 alkyl radical, where alkyl is defined as above. "Haloalkylsulfonyl", embraces haloalkyl radicals attached to a sulfonyl radical, where haloalkyl is defined as above. "Haloalkylsulfonylalkyl", embraces haloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "aminosulfonyl" denotes an amino radical attached to a sulfonyl radical.

20 The term "sulfinyl", whether used alone or linked to other terms such as alkylsulfinyl, denotes respectively divalent radicals $-S(O)-$. "Alkylsulfinyl", embraces alkyl radicals attached to a sulfinyl radical, where alkyl is defined as above. "Alkylsulfinylalkyl", embraces alkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. "Haloalkylsulfinyl", embraces

25 haloalkyl radicals attached to a sulfinyl radical, where haloalkyl is defined as above. "Haloalkylsulfinylalkyl", embraces haloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to

30 alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The terms benzyl and phenylmethyl are interchangeable.

The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals wherein the heteroaralkyl radical may be additionally substituted with three or

35 more substituents as defined above for aralkyl radicals. The term

"perhaloaralkyl" embraces aryl-substituted alkyl radicals wherein the aralkyl radical is substituted with three or more halo radicals as defined above.

The term "aralkylsulfinyl", embraces aralkyl radicals attached to a sulfinyl radical, where aralkyl is defined as above. "Aralkylsulfinylalkyl",
5 embraces aralkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aralkylsulfonyl", embraces aralkyl radicals attached to a sulfonyl radical, where aralkyl is defined as above. "Aralkylsulfonylalkyl",
10 embraces aralkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "cycloalkyl" embraces radicals having three to 15 carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term
15 cycloalkyl embraces radicals having seven to 15 carbon atoms and having two to four rings. Examples include radicals such as norbornyl (i.e., bicyclo[2.2.1]heptyl) and adamantyl. The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl
20 radicals having one to six carbon atoms. Examples of such radicals include cyclohexylhexyl. The term "cycloalkenyl" embraces radicals having three to ten carbon atoms and one or more carbon-carbon double bonds. Preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclobutenyl, cyclopentenyl,
25 cyclohexenyl and cycloheptenyl. The term "halocycloalkyl" embraces radicals wherein any one or more of the cycloalkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkyl, dihalocycloalkyl and polyhalocycloalkyl radicals. A monohalocycloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom
30 within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhalocycloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred halocycloalkyl radicals are "lower halocycloalkyl" radicals having three to about eight carbon atoms. Examples of
35 such halocycloalkyl radicals include fluorocyclopropyl, difluorocyclobutyl,

trifluorocyclopentyl, tetrafluorocyclohexyl, and dichlorocyclopropyl. The term "halocycloalkenyl" embraces radicals wherein any one or more of the cycloalkenyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkenyl, dihalocycloalkenyl and polyhalocycloalkenyl radicals.

The term "cycloalkoxy" embraces cycloalkyl radicals attached to an oxy radical. Examples of such radicals includes cyclohexoxy and cyclopentoxy. The term "cycloalkoxyalkyl" also embraces alkyl radicals having one or more cycloalkoxy radicals attached to the alkyl radical, that is, to form monocycloalkoxyalkyl and dicycloalkoxyalkyl radicals. Examples of such radicals include cyclohexoxyethyl. The "cycloalkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "halocycloalkoxy" and "halocycloalkoxyalkyl" radicals.

The term "cycloalkylalkoxy" embraces cycloalkyl radicals attached to an alkoxy radical. Examples of such radicals includes cyclohexylmethoxy and cyclopentylmethoxy.

The term "cycloalkenyloxy" embraces cycloalkenyl radicals attached to an oxy radical. Examples of such radicals includes cyclohexenyloxy and cyclopentenylloxy. The term "cycloalkenyloxyalkyl" also embraces alkyl radicals having one or more cycloalkenyloxy radicals attached to the alkyl radical, that is, to form monocycloalkenyloxyalkyl and dicycloalkenyloxyalkyl radicals. Examples of such radicals include cyclohexenyloxyethyl. The "cycloalkenyloxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "halocycloalkenyloxy" and "halocycloalkenyloxyalkyl" radicals.

The term "cycloalkylenedioxy" radicals denotes cycloalkylene radicals having at least two oxygens bonded to a single cycloalkylene group. Examples of "alkylenedioxy" radicals include 1,2-dioxycyclohexylene.

The term "cycloalkylsulfinyl", embraces cycloalkyl radicals attached to a sulfinyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfinylalkyl", embraces cycloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "Cycloalkylsulfonyl", embraces cycloalkyl radicals attached to a sulfonyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfonylalkyl", embraces cycloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "cycloalkylalkanoyl" embraces radicals wherein one or more of the cycloalkyl carbon atoms are substituted with one or more carbonyl radicals as defined below. Specifically embraced are monocarbonylcycloalkyl and dicarbonylcycloalkyl radicals. Examples of monocarbonylcycloalkyl radicals include cyclohexylcarbonyl, cyclohexylacetyl, and cyclopentylcarbonyl. Examples of dicarbonylcycloalkyl radicals include 1,2-dicarbonylcyclohexane.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having one to six carbon atoms. An example of "lower alkylthio" is methylthio ($\text{CH}_3\text{-S-}$). The "alkylthio" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkylthio" radicals. Examples of such radicals include fluoromethylthio, chloromethylthio, trifluoromethylthio, difluoromethylthio, trifluoroethylthio, fluoroethylthio, tetrafluoroethylthio, pentafluoroethylthio, and fluoropropylthio.

The term "alkyl aryl amino" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, and one aryl radical both attached to an amino radical. Examples include N-methyl-4-methoxyaniline, N-ethyl-4-methoxyaniline, and N-methyl-4-trifluoromethoxyaniline.

The terms alkylamino denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical.

The terms arylamino denotes "monoarylamino" and "diarylamino" containing one or two aryl radicals, respectively, attached to an amino radical. Examples of such radicals include N-phenylamino and N-naphthylamino.

The term "aralkylamino", embraces aralkyl radicals attached to an amino radical, where aralkyl is defined as above. The term aralkylamino denotes "monoaralkylamino" and "diaralkylamino" containing one or two aralkyl radicals, respectively, attached to an amino radical. The term aralkylamino further denotes "monoaralkyl monoalkylamino" containing one aralkyl radical and one alkyl radical attached to an amino radical.

The term "arylsulfinyl" embraces radicals containing an aryl radical, as defined above, attached to a divalent S(O) atom. The term "arylsulfinylalkyl" denotes arylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms.

The term "arylsulfonyl", embraces aryl radicals attached to a sulfonyl radical, where aryl is defined as above. "arylsulfonylalkyl", embraces arylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "heteroarylsulfinyl" embraces radicals containing an heteroaryl radical, as defined above, attached to a divalent S(O) atom. The term "heteroarylsulfinylalkyl" denotes heteroarylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms. The term "Heteroarylsulfonyl", embraces heteroaryl radicals attached to a sulfonyl radical, where heteroaryl is defined as above. "Heteroarylsulfonylalkyl", embraces heteroarylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy, 4-chloro-3-ethylphenoxy, 4-chloro-3-methylphenoxy, 3-chloro-4-ethylphenoxy, 3,4-dichlorophenoxy, 4-methylphenoxy, 3-trifluoromethoxyphenoxy, 3-trifluoromethylphenoxy, 4-fluorophenoxy, 3,4-dimethylphenoxy, 5-bromo-2-fluorophenoxy, 4-bromo-3-fluorophenoxy, 4-fluoro-3-methylphenoxy, 5,6,7,8-tetrahydronaphthyloxy, 3-isopropylphenoxy, 3-cyclopropylphenoxy, 3-ethylphenoxy, 3-pentafluoroethylphenoxy, 3-(1,1,2,2-tetrafluoroethoxy)-phenoxy, and 4-*tert*-butylphenoxy.

The term "aroyl" embraces aryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include benzoyl and toluoyl.

The term "aralkanoyl" embraces aralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, phenylacetyl.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. Examples of such radicals include benzyloxy, 1-phenylethoxy, 3-trifluoromethoxybenzyloxy, 3-trifluoromethylbenzyloxy, 3,5-difluorobenzyloxy, 3-bromobenzyloxy, 4-propylbenzyloxy, 2-fluoro-3-trifluoromethylbenzyloxy, and 2-phenylethoxy.

The term "aryloxyalkyl" embraces aryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenoxymethyl.

The term "haloaryloxyalkyl" embraces aryloxyalkyl radicals, as defined above, wherein one to five halo radicals are attached to an aryloxy group.

The term "heteroaroyl" embraces heteroaryl radicals, as defined above, attached to a carbonyl radical as defined above. Examples of such radicals include furoyl and nicotinyl.

The term "heteroaralkanoyl" embraces heteroaralkyl radicals, as defined herein, attached to a carbonyl radical as defined above. Examples of such radicals include, for example, pyridylacetyl and furylbutyryl.

The term "heteroaralkoxy" embraces oxy-containing heteroaralkyl radicals attached through an oxygen atom to other radicals. More preferred heteroaralkoxy radicals are "lower heteroaralkoxy" radicals having heteroaryl radicals attached to lower alkoxy radical as described above.

The term "haloheteroaryloxyalkyl" embraces heteroaryloxyalkyl radicals, as defined above, wherein one to four halo radicals are attached to an heteroaryloxy group.

The term "heteroarylamino" embraces heterocyclyl radicals, as defined above, attached to an amino group. Examples of such radicals include pyridylamino.

The term "heteroarylaminoalkyl" embraces heteroarylamino radicals, as defined above, attached to an alkyl group. Examples of such radicals include pyridylmethylamino.

The term "heteroaryloxy" embraces heterocyclyl radicals, as defined above, attached to an oxy group. Examples of such radicals include 2-thiophenyloxy, 2-pyrimidyloxy, 2-pyridyloxy, 3-pyridyloxy, and 4-pyridyloxy.

The term "heteroaryloxyalkyl" embraces heteroaryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include 2-pyridyloxymethyl, 3-pyridyloxyethyl, and 4-pyridyloxymethyl.

The term "arylthio" embraces aryl radicals, as defined above, attached to a sulfur atom. Examples of such radicals include phenylthio.

The term "arylthioalkyl" embraces arylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenylthiomethyl.

The term "alkylthioalkyl" embraces alkylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include

C-3203

methylthiomethyl. The term "alkoxyalkyl" embraces alkoxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include methoxymethyl.

The term "carbonyl" denotes a carbon radical having two of the four
 5 covalent bonds shared with an oxygen atom. The term "carboxy" embraces a hydroxyl radical, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboxamide" embraces amino, monoalkylamino, dialkylamino, monocycloalkylamino, alkylcycloalkylamino, and dicycloalkylamino radicals, attached to one of two unshared bonds in a carbonyl group. The term
 10 "carboxamidoalkyl" embraces carboxamide radicals, as defined above, attached to an alkyl group. The term "carboxyalkyl" embraces a carboxy radical, as defined above, attached to an alkyl group. The term "carboalkoxy" embraces alkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboaralkoxy" embraces aralkoxy radicals, as defined above,
 15 attached to one of two unshared bonds in a carbonyl group. The term "monocarboalkoxyalkyl" embraces one carboalkoxy radical, as defined above, attached to an alkyl group. The term "dicarboalkoxyalkyl" embraces two carboalkoxy radicals, as defined above, attached to an alkylene group. The term "monocyanoalkyl" embraces one cyano radical, as defined above, attached to an
 20 alkyl group. The term "dicyanoalkylene" embraces two cyano radicals, as defined above, attached to an alkyl group. The term "carboalkoxycyanoalkyl" embraces one cyano radical, as defined above, attached to an carboalkoxyalkyl group.

The term "acyl", alone or in combination, means a carbonyl or
 25 thionocarbonyl group bonded to a radical selected from, for example, hydrido, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, alkoxyalkyl, haloalkoxy, aryl, heterocyclyl, heteroaryl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, alkylthio, arylthio, amino, alkylamino, dialkylamino, aralkoxy, arylthio, and alkylthioalkyl. Examples of "acyl" are formyl, acetyl, benzoyl, trifluoroacetyl, phthaloyl, malonyl, nicotinyl, and the like.
 30 The term "haloalkanoyl" embraces one or more halo radicals, as defined herein, attached to an alkanoyl radical as defined above. Examples of such radicals include, for example, chloroacetyl, trifluoroacetyl, bromopropanoyl, and heptafluorobutanoyl.

The term "phosphono" embraces a pentavalent phosphorus attached with
 35 two covalent bonds to an oxygen radical. The term "dialkoxyphosphono" denotes

two alkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "diaralkoxyphosphono" denotes two aralkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "dialkoxyphosphonoalkyl" denotes dialkoxyphosphono radicals, as defined
 5 above, attached to an alkyl radical. The term "diaralkoxyphosphonoalkyl" denotes diaralkoxyphosphono radicals, as defined above, attached to an alkyl radical.

The term "amino" denotes a nitrogen atom containing two substituents such as hydrido, hydroxy or alkyl and having one covalent bond available for bonding to a single atom such as carbon. Examples of such amino radicals include, for

10 example, -NH_2 , -NHCH_3 , -NHOH , and -NHOCH_3 . The term "imino" denotes a nitrogen atom containing one substituent such as hydrido, hydroxy or alkyl and having two covalent bonds available for bonding to a single atom such as carbon. Examples of such imino radicals include, for example, =NH , =NCH_3 , =NOH , and =NOCH_3 . The term "imino carbonyl" denotes a carbon radical having two of
 15 the four covalent bond sites shared with an imino group. Examples of such imino carbonyl radicals include, for example, C=NH , C=NCH_3 , C=NOH , and

C=NOCH_3 . The term "amidino" embraces a substituted or unsubstituted amino group bonded to one of two available bonds of an iminocarbonyl radical. Examples of such amidino radicals include, for example, $\text{NH}_2\text{-C=NH}$, $\text{NH}_2\text{-C=NCH}_3$,

20 $\text{NH}_2\text{-C=NOCH}_3$ and $\text{CH}_3\text{NH-C=NOH}$. The term "guanidino" denotes an amidino group bonded to an amino group as defined above where said amino group can be bonded to a third group. Examples of such guanidino radicals include, for example, $\text{NH}_2\text{-C(NH)-NH-}$, $\text{NH}_2\text{-C(NCH}_3\text{)-NH-}$, $\text{NH}_2\text{-C(NOCH}_3\text{)-NH-}$, and $\text{CH}_3\text{NH-C(NOCH}_3\text{)-NH-}$.

25 The term "sulfonium" denotes a positively charged trivalent sulfur atom where said sulfur is substituted with three carbon based groups such as alkyl, alkenyl, aralkyl, or aryl. The term "dialkyl sulfonium" denotes a sulfonium group where said sulfur is substituted with two alkyl groups. Examples of such dialkylsulfonium radicals include, for example, $(\text{CH}_3)_2\text{S}^+$. The term "dialkyl

sulfonium alkyl" denotes a dialkyl sulfonium group where said group is bonded to one bond of an alkylene group as defined above. Examples of such

dialkylsulfoniumalkyl radicals include $(\text{CH}_3)_2\text{S}^+-\text{CH}_2\text{CH}_2-$.

- The term "phosphonium" denotes a positively charged tetravalent
- 5 phosphorus atom where said phosphorus is substituted with four carbon based groups such as alkyl, alkenyl, aralkyl, or aryl. The term "trialkyl phosphonium" denotes a phosphonium group where said phosphorus is substituted with three alkyl groups. Examples of such trialkylphosphonium radicals include, for example, $(\text{CH}_3)_3\text{P}^+$.
- 10 Said "alkyl", "alkenyl", "alkynyl", "alkanoyl", "alkylene", "alkenylene", "hydroxyalkyl", "haloalkyl", "haloalkylene", "haloalkenyl", "alkoxy", "alkenyloxy", "alkenyloxyalkyl", "alkoxyalkyl", "aryl", "perhaloaryl", "haloalkoxy", "haloalkoxyalkyl", "haloalkenyloxy", "haloalkenyloxyalkyl", "alkylenedioxy", "haloalkylenedioxy", "heterocyclyl", "heteroaryl",
- 15 "hydroxyhaloalkyl", "alkylsulfonyl", "haloalkylsulfonyl", "alkylsulfonylalkyl", "haloalkylsulfonylalkyl", "alkylsulfinyl", "alkylsulfinylalkyl", "haloalkylsulfinylalkyl", "aralkyl", "heteroaralkyl", "perhaloaralkyl", "aralkylsulfonyl", "aralkylsulfonylalkyl", "aralkylsulfinyl", "aralkylsulfinylalkyl", "cycloalkyl", "cycloalkylalkanoyl", "cycloalkylalkyl", "cycloalkenyl",
- 20 "halocycloalkyl", "halocycloalkenyl", "cycloalkylsulfinyl", "cycloalkylsulfinylalkyl", "cycloalkylsulfonyl", "cycloalkylsulfonylalkyl", "cycloalkoxy", "cycloalkoxyalkyl", "cycloalkylalkoxy", "cycloalkenyloxy", "cycloalkenyloxyalkyl", "cycloalkylenedioxy", "halocycloalkoxy", "halocycloalkoxyalkyl", "halocycloalkenyloxy", "halocycloalkenyloxyalkyl",
- 25 "alkylthio", "haloalkylthio", "alkylsulfinyl", "amino", "oxy", "thio", "alkylamino", "arylamino", "aralkylamino", "arylsulfinyl", "arylsulfinylalkyl", "arylsulfonyl", "arylsulfonylalkyl", "heteroarylsulfinyl", "heteroarylsulfinylalkyl", "heteroarylsulfonyl", "heteroarylsulfonylalkyl", "heteroarylamino", "heteroarylaminoalkyl", "heteroaryloxy", "heteroaryloxyalkyl", "aryloxy",
- 30 "aroyle", "aralkanoyl", "aralkoxy", "aryloxyalkyl", "haloaryloxyalkyl", "heteroaroyl", "heteroaralkanoyl", "heteroaralkoxy", "heteroaralkoxyalkyl", "arylthio", "arylthioalkyl", "alkoxyalkyl", "acyl", "amidino", "guanidino", "dialkylsulfonium", "trialkylphosphonium", and "dialkylsulfoniumalkyl" groups defined above may optionally have 1 or more non-hydrido substituents such as

- amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroaryl-amino, N-heteroaryl-amino-N-alkyl-amino, heteroaryl-aminoalkyl, heteroaryl-oxy, heteroaryl-oxyalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkyl-amino, alkylthio, alkylthioalkyl, aryl-amino, aralkyl-amino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroaryl-sulfinylalkyl, heteroaryl-sulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, aminoalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryl-oxy, heteroaryl-oxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarbonyl, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carb haloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl.
- 30 The term "spacer" can include a covalent bond and a linear moiety having a backbone of 1 to 7 contiguous atoms. The spacer may have 1 to 7 atoms of a univalent or multi-valent chain. Univalent chains may be constituted by a radical selected from $=C(H)-$, $=C(R^{2a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-NH-$, $-N(R^{2a})-$, $-N=$, $-CH(OH)-$, $=C(OH)-$, $-CH(OR^{2a})-$, $=C(OR^{2a})-$, and

- C(O)- wherein R^{2a} is selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, perhaloaralkyl, heteroarylalkyl, heteroaryloxyalkyl, heteroarylthioalkyl, and heteroarylalkenyl.
- 5 Multi-valent chains may consist of a straight chain of 1 or 2 or 3 or 4 or 5 or 6 or 7 atoms or a straight chain of 1 or 2 or 3 or 4 or 5 or 6 atoms with a side chain. The chain may be constituted of one or more radicals selected from: lower alkylene, lower alkenyl, -O-, -O-CH₂-, -S-CH₂-, -CH₂CH₂-, ethenyl, -CH=CH(OH)-, -OCH₂O-, -O(CH₂)₂O-, -NHCH₂-, -OCH(R^{2a})O-,
- 10 -O(CH₂CHR^{2a})O-, -OCF₂O-, -O(CF₂)₂O-, -S-, -S(O)-, -S(O)₂-, -N(H)-, -N(H)O-, -N(R^{2a})O-, -N(R^{2a})-, -C(O)-, -C(O)NH-, -C(O)NR^{2a}-, -N=, -OCH₂-, -SCH₂-, S(O)CH₂-, -CH₂C(O)-, -CH(OH)-, =C(OH)-, -CH(OR^{2a})-, =C(OR^{2a})-, S(O)₂CH₂-, and -NR^{2a}CH₂- and many other radicals defined above or generally known or ascertained by one of skill-in-the art. Side chains may
- 15 include substituents such as 1 or more non-hydrido substituents such as amidino, guanidino, dialkylsulfonium, trialkylphosphonium, dialkylsulfoniumalkyl, perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl,
- 20 heteroarylamino, N-heteroarylamino-N-alkylamino, heteroarylaminomethyl, heteroaryloxy, heteroaryloxyalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy,
- 25 halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl,
- 30 alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido,

diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalkyl, alkylenedioxy, haloalkylenedioxy, 5 cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, aminoalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, 10 heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl.

Compounds of the present invention can exist in tautomeric, geometric or 15 stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention.

Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric 20 forms are also included within the invention.

The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans").

25 Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms.

Some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures of R and S forms for each stereocenter present.

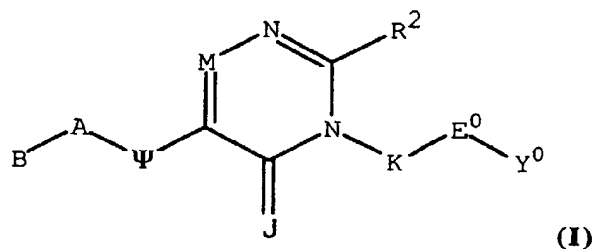
30 Some of the compounds described herein may contain one or more ketonic or aldehydic carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally in the "keto" form and in part or principally as one or more "enol" forms of each aldehyde and ketone group present. Compounds of the present

invention having aldehydic or ketonic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms.

Some of the compounds described herein may contain one or more amide carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally in the "keto" form and in part or principally as one or more "enol" forms of each amide group present. Compounds of the present invention having amidic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms. Said amide carbonyl groups may be both oxo (C=O) and thiono (C=S) in type.

Some of the compounds described herein may contain one or more imine or enamine groups or combinations thereof. Such groups may exist in part or principally in the "imine" form and in part or principally as one or more "enamine" forms of each group present. Compounds of the present invention having said imine or enamine groups are meant to include both "imine" and "enamine" tautomeric forms.

The present invention also comprises a treatment and prophylaxis in anticoagulant therapy for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular disease in a subject, comprising administering to the subject having such disorder a therapeutically-effective amount of a compound of Formula (I):



or a pharmaceutically-acceptable salt thereof.

As a further embodiment, compounds of the present invention of Formula (I) or a pharmaceutically-acceptable salt thereof as defined above, comprise a treatment and prophylaxis of coronary artery disease, cerebrovascular disease and other coagulation cascade related disorders in a subject, comprising administering to the subject having such disorder a therapeutically-effective amount of compounds of formula (I) of the present invention or a pharmaceutically-acceptable salt thereof.

Compounds of the present invention of Formula (I) or a pharmaceutically-acceptable salt thereof can also be used whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus coagulation inhibitors of the present invention can be added to or contacted with stored whole blood and any medium containing or suspected of containing plasma coagulation factors and in which it is desired that blood coagulation be inhibited, e.g. when contacting the mammal's blood with material selected from the group consisting of vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems.

Compounds of Formula (I) are capable of inhibiting activity of serine proteases related to the coagulation cascade, and thus could be used in the manufacture of a medicament, a method for the prophylactic or therapeutic treatment of diseases mediated by coagulation cascade serine proteases, such as inhibiting the formation of blood platelet aggregates, inhibiting the formation of fibrin, inhibiting thrombus formation, and inhibiting embolus formation in a mammal, in blood, in blood products, and in mammalian organs. The compounds also can be used for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels in a mammal. The compounds also can be used to study the mechanism of action of coagulation cascade serine proteases to enable the design of better inhibitors and development of better assay methods. The compounds of Formula (I) would be also useful in prevention of cerebral vascular accident (CVA) or stroke.

Also included in the family of compounds of Formula (I) are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salt" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula (I) may be prepared from inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric,

carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, 5 ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula (I) 10 include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding 15 compound of Formula (I) by reacting, for example, the appropriate acid or base with the compound of Formula (I).

The present invention also comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formulas (I) in association with at least one pharmaceutically-acceptable carrier, adjuvant or 20 diluent. Pharmaceutical compositions of the present invention can comprise the active compounds of Formula (I) in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be 25 administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended.

The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, 30 intramuscularly, ocularly, or topically. For treating ocular build up of fibrin, the compounds may be administered intraocularly or topically as well as orally or parenterally.

The compounds can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a 35 sustained release of the active ingredient. The active ingredient can be

compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other silicon containing polymers.

5 The compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

10 The compounds may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues.
15 Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or
20 amphiphathic block copolymers of hydrogels.

For oral administration, the pharmaceutical composition may be in the form of, for example, tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, liquids including syrups, and emulsions. The
25 pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

30 The amount of therapeutically active compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the
35 particular compound employed, and thus may vary widely.

The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, and preferably in the range of about 0.5 to 500 mg. A daily dose of about 0.01 to 100 mg/kg body weight, and preferably between about 0.5 and about 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

The compounds may be formulated in topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base.

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as diisoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

138

In practicing the methods of the present invention for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular disease, the compounds and pharmaceutical compositions of the present invention are administered alone or in combination with one
5 another, or in combination with other therapeutics or in vivo diagnostic agents. The coagulation cascade inhibitors of the present invention can also be co-administered with suitable anti-platelet aggregation agents, including, but not limited to ticlopidine or clopidogrel, fibrinogen receptor antagonists (e.g. to
10 treat or prevent unstable angina or to prevent reocclusion after angioplasty and restenosis), anti-coagulants such as aspirin, warfarin or heparins, thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various pathologies, lipid lowering agents including antihypercholesterolemics (e.g. HMG CoA reductase inhibitors such as
15 mevastatin, lovastatin, simvastatin, pravastatin, and fluvastatin, HMG CoA synthetase inhibitors, etc.), anti-diabetic drugs, or other cardiovascular agents (loop diuretics, thiazide type diuretics, nitrates, aldosterone antagonists (i.e., spironolactone and epoxymexlerenone), angiotensin converting enzyme (e.g.
20 ACE) inhibitors, angiotensin II receptor antagonists, beta-blockers, antiarrhythmics, anti-hypertension agents, and calcium channel blockers) to treat or prevent atherosclerosis. For example, patients suffering from coronary artery disease, and patients subjected to angioplasty procedures, would benefit from coadministration of fibrinogen receptor antagonists and coagulation
25 cascade inhibitors of the present invention. Also, coagulation cascade inhibitors could enhance the efficiency of tissue plasminogen activator-mediated thrombolytic reperfusion.

Typical doses of coagulation cascade inhibitors of the present invention with other suitable anti-platelet agents, anticoagulation agents, cardiovascular therapeutic agents, or thrombolytic agents may be the same as those doses of coagulation cascade inhibitors administered without coadministration of
30 additional anti-platelet agents, anticoagulation agents, cardiovascular therapeutic agents, or thrombolytic agents, or may be substantially less than those doses of coagulation cascade inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, cardiovascular therapeutic agents, or thrombolytic agents, depending on a
35 patient's therapeutic needs.

All mentioned references are incorporated by reference as if here written.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Without further elaboration, it is believed that one skilled in the art can, using the preceding descriptions, utilize the present invention to its fullest extent. Therefore the following preferred specific embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever. Compounds containing multiple variations of the structural modifications illustrated in the schemes or the following Examples are also contemplated. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

One skilled in the art may use these generic methods to prepare the following specific examples, which have been or may be properly characterized by ¹H NMR, mass spectrometry, elemental composition, and similar procedures. These compounds also may be formed in vivo.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula (I). These detailed descriptions fall within the scope and are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are Degrees centigrade unless otherwise indicated.

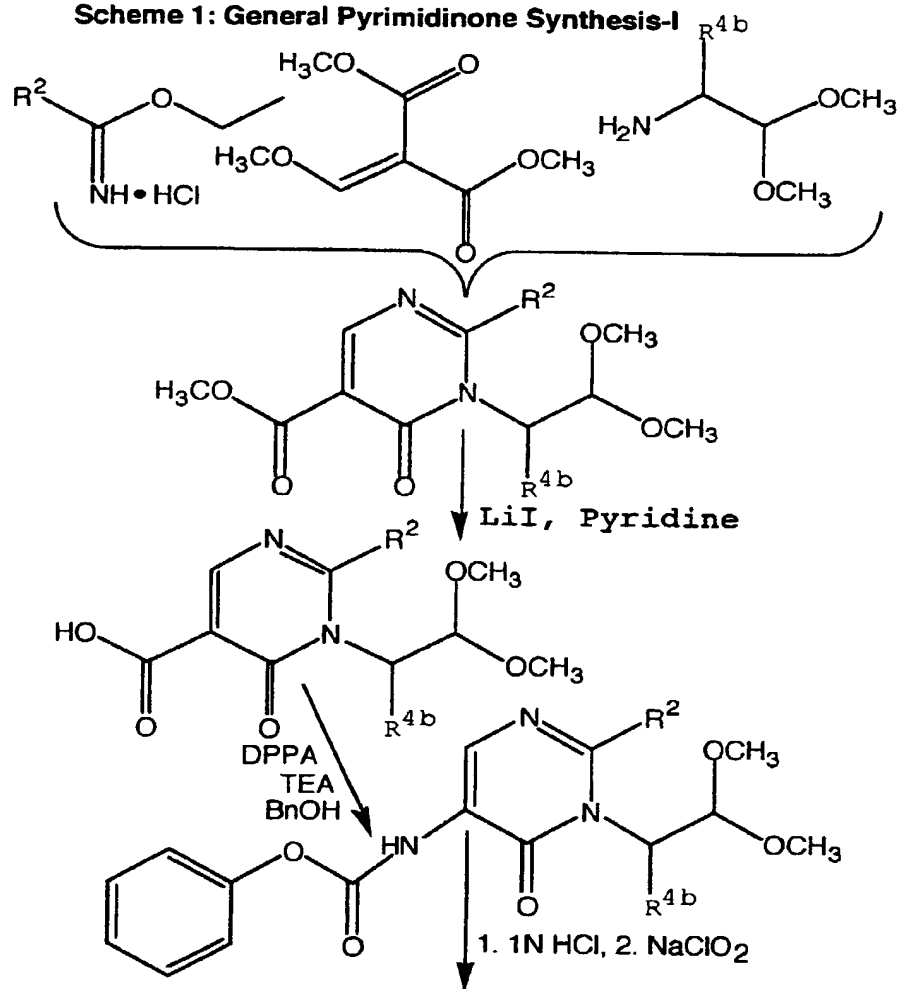
The following general synthetic sequences are useful in making the present invention. Abbreviations used in the schemes and tables include: "AA" represents amino acids, "AcCN" represents acetonitrile, "AcOH" represents acetic acid, "BINAP" represents 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, "BnOH" represents benzyl alcohol, "BnCHO" represents 2-phenylethanal, "BnSO₂Cl" represents benzylsulfonyl chloride, "Boc" represents tert-butyloxycarbonyl, "BOP" represents benzotriazol-1-yl-oxy-tris-(dimethylamino), "bu" represents butyl, "dba" represents dibenzylidene-acetone, "DCC" represents 1,3-dicyclohexylcarbodiimide, "DCM" represents dichloromethane or methylene chloride, "DIBAH" or "DIBAL" represents diisobutylaluminum hydride, "DMF" represents dimethylformamide, "DMSO"

- represents dimethylsulfoxide, "DPPA" represents diphenylphosphoryl azide",
 "EDC" represents 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
 hydrochloride, "Ex. No." represents Example Number, "Fmoc" represents 9-
 fluorenylmethoxycarbonyl, "HOBt" represents hydroxybenzotriazole", "LDA"
 5 represents lithium diisopropylamide, "MW" represents molecular weight,
 "NMM" represents N-methylmorpholine, "Ph" represents phenyl or aryl,
 "PHTH" represents a phthaloyl group, "pnZ" represents 4-nitrobenzyloxy-
 carbonyl, "PTC" represents a phase transfer catalyst, "py" represents pyridine,
 "RNH₂" represents a primary organic amine, "SEM" represents 2-
 10 (trimethylsilyl)ethoxy-methyl chloride, "p-TsOH" represents
 paratoluenesulfonic acid, "TBAF" represents tetrabutylammonium fluoride,
 "TBTU" represents 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl uronium
 tetrafluoroborate, "TEA" represents triethylamine, "TFA" represents
 trifluoroacetic acid, "THF" represents tetrahydrofuran, "TMS" represents
 15 trimethylsilyl, "TMSCN" represents trimethylsilyl cyanide, and "Cbz" or "Z"
 represents benzyloxycarbonyl.

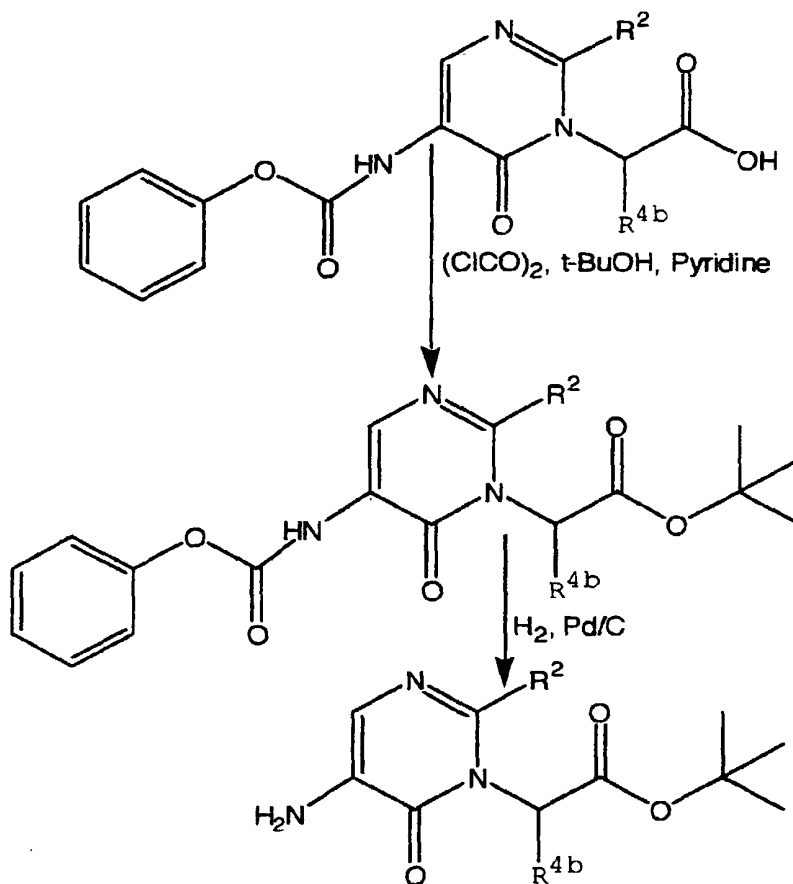
GENERAL SYNTHETIC PROCEDURES AND SPECIFIC EXAMPLES

- 20 The compounds of the present invention can be synthesized, for example,
 according to the following procedures and Schemes given below.

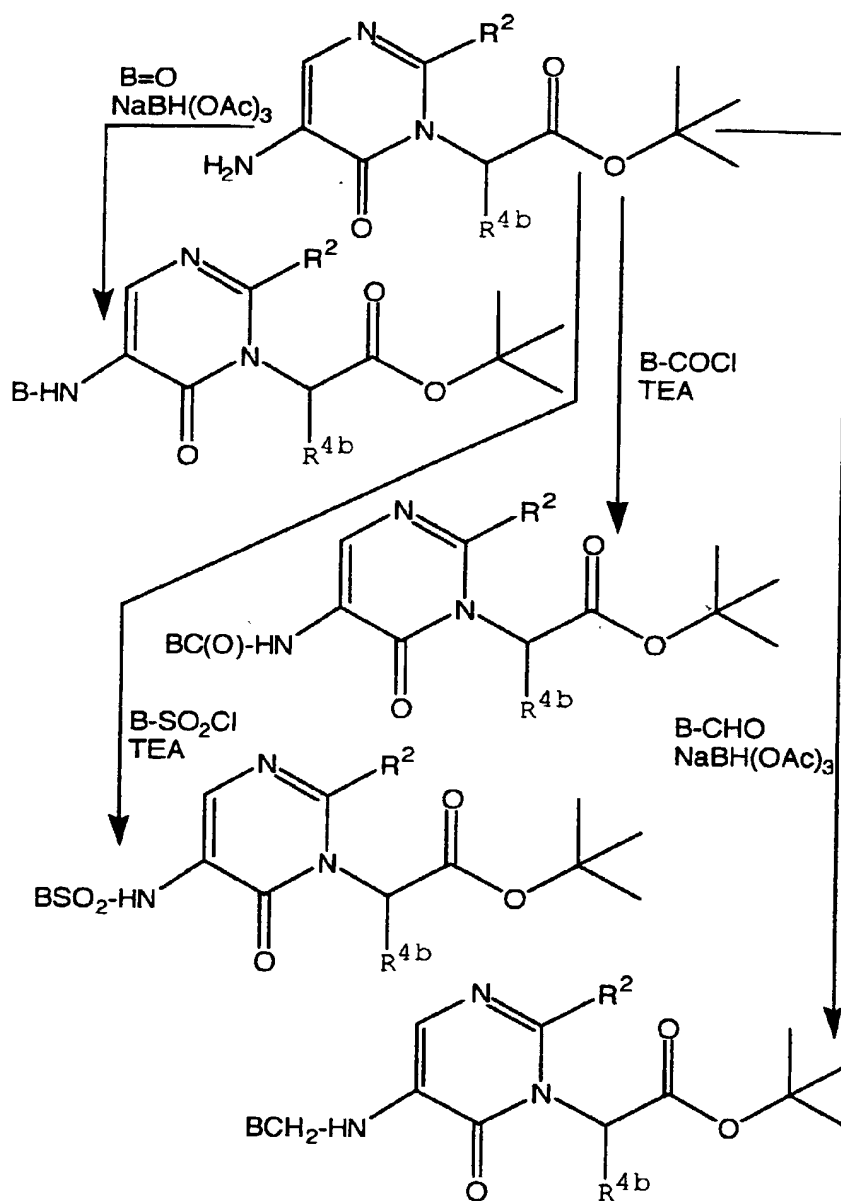
- A general synthetic approach to a wide variety of R²-substituted
 pyrimidinones is shown in **Schemes 1** through **Scheme 5** below. Treatment of
 a solution of ethyl benzimidate hydrochloride in methanol with aminoacetaldehyde
 25 dimethyl acetal provided the substituted benzamidine. Cyclization of the
 benzamidine with dimethyl methoxymethylene-malonate resulted in the formation
 of the pyrimidinone heterocyclic core with the required functional groups for
 further manipulation. Demethylation of the ester with lithium iodide followed by
 Curtius rearrangement of the resulting acid installed the crucial nitrogen at C-5 as a
 30 protected carbamate. Hydrolysis of the dimethyl acetal and oxidation of the
 resulting aldehyde with sodium chlorite gave the glycine unit at N-3. Protection of
 the acid as a t-butyl ester followed by deprotection of carbamate by hydrogenation
 gave the free amine at C-5. Treatment of this amine with a sulfonyl chloride or
 with an aldehyde under reductive amination conditions gave the sulfonamide or

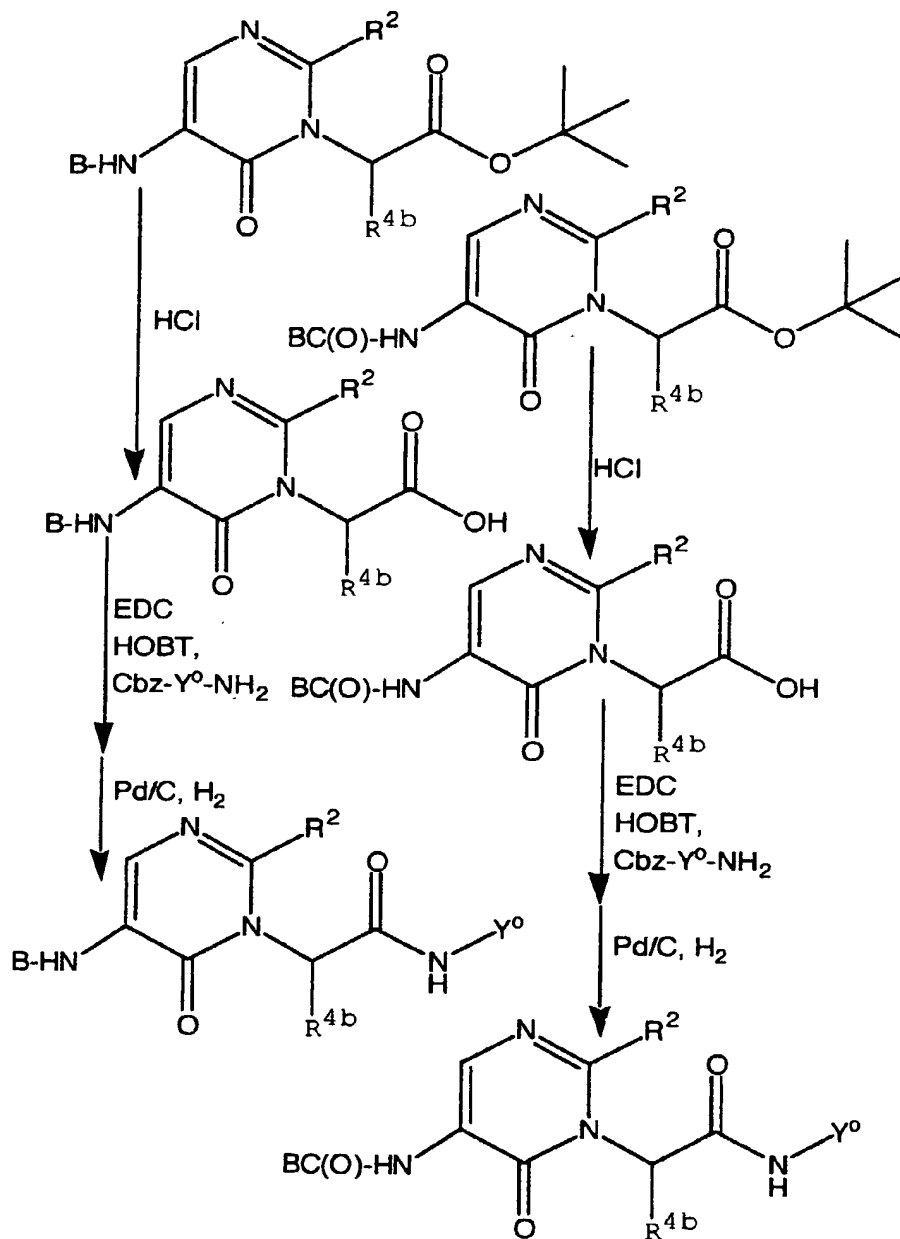
Scheme 1: General Pyrimidinone Synthesis-I

Scheme 2: General Pyrimidinone Synthesis-I (Continued)

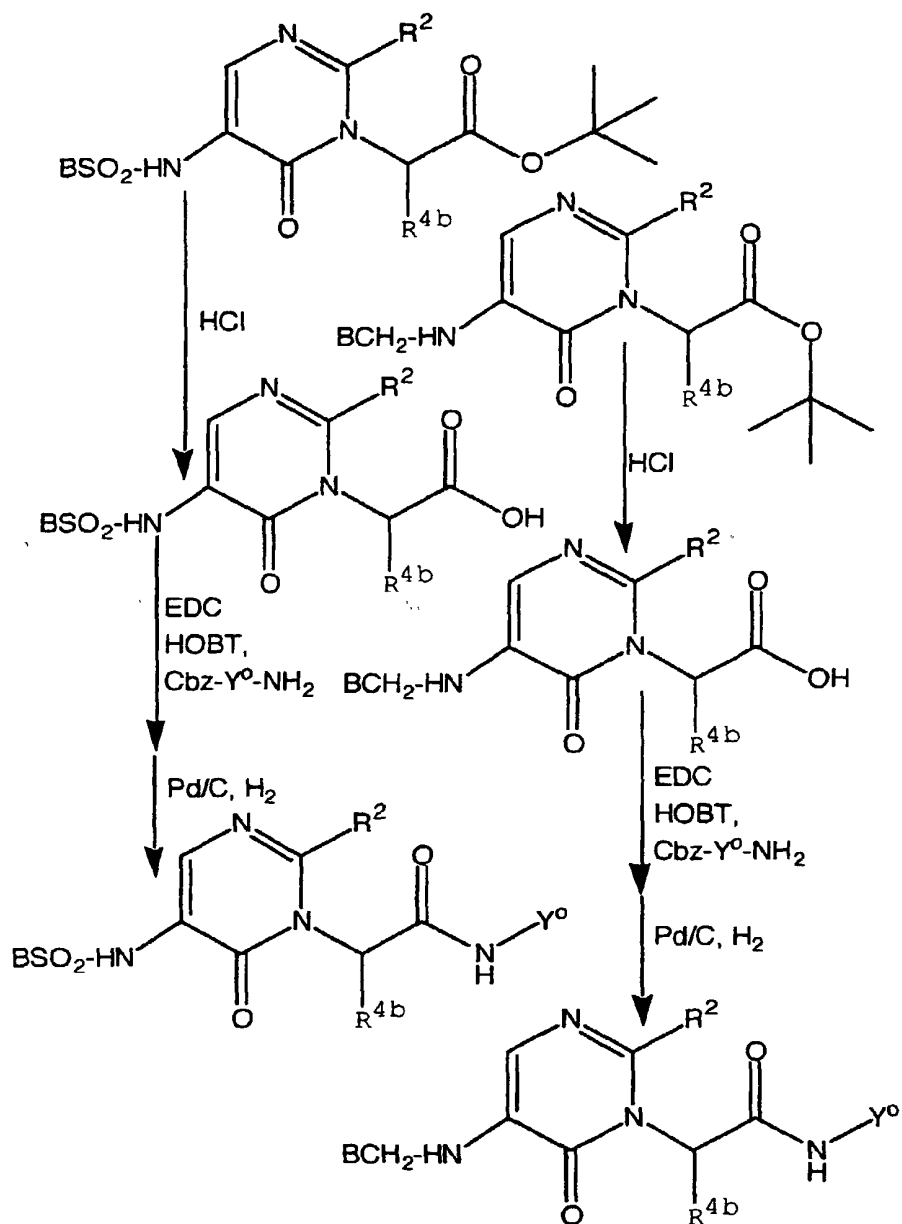


Scheme 3: General Pyrimidinone Synthesis-I (Continued)

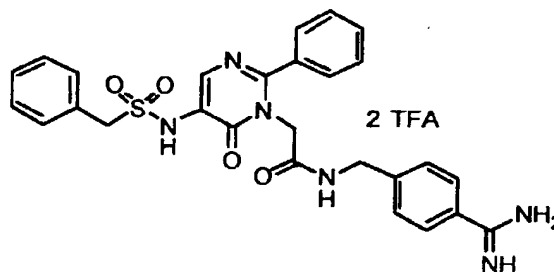


Scheme 4: General Pyrimidinone Synthesis-I (Concluded)

Scheme 5: General Pyrimidinone Synthesis-I (Concluded)



Synthetic Scheme 1 through Scheme 5 are exemplified in the following examples.

Example 1

- (EX-1A) A solution of ethyl benzimidate hydrochloride (92.25 g, 496.9 mmol) in 300.0 mL dry methanol (1.68 M) was cooled to ca 0°C and added a
- 5 solution of aminoacetaldehyde dimethyl acetal (73.10 mL, 670.9 mmol) in dry methanol (75.0 mL, 9.0 M) drop wise at such a rate the temperature was kept below 5°C. The resulting solution was allowed to stir for 3 days with the temperature being maintained below 5°C. The reaction mixture was then concentrated under reduced pressure to give a yellow oil. The residue was
- 10 dissolved in 1 N NaOH (750 mL) and extracted with dichloromethane (4 x 250 mL). The organic solutions were combined, dried (MgSO₄), and concentrated to give 108.13 g crude N-(2,2-dimethoxyethyl)benzamidinium as a yellow oil. The crude N-(2,2-dimethoxyethyl)benzamidinium (108.13 g, 519.2 mmol) in dry methanol (125.0 mL, 4.2 M) was added dimethyl methoxymethylenemalonate
- 15 (94.13 g, 540.5 mmol) in one portion at room temperature. The resulting mixture was heated to approximately 100°C, where the solvent was slowly distilled off over a two hour period. The resulting dark brown solution was allowed to cool to room temperature and was diluted ethyl acetate (1 L). The organic solution was washed with saturated NH₄Cl (2 x 500 mL) and brine (1 x 500 ml). The organic
- 20 solution was dried (MgSO₄), filtered and concentrated. Purification of the crude product by MPLC (25% ethyl acetate/hexane) gave pure methyl 1-(2,2-dimethoxyethyl)-2-phenylpyrimidin-6(1H)-one-5-carboxylate (EX-1A) in 73% yield as a tan oil: ¹H NMR (300 MHz, CDCl₃) δ 8.73 (s, 1H), 7.59-7.49 (m, 5H), 4.86 (t, J = 5.5 Hz, 1H), 4.16 (d, J = 5.4 Hz, 2H), 3.95 (s, 3H), 3.32 (s, 6H);
- 25 ¹³C NMR (75 MHz, CDCl₃) δ 165.9, 164.6, 159.3, 158.2, 134.6, 130.9, 128.93, 128.78, 114.9, 101.4, 56.0, 55.1, 52.7, 49.1; HRMS (ES) calcd for C₁₆H₁₉N₂O₅ 319.1294, found 319.1288.

(EX-1B) A solution of methyl 1-(2,2-dimethoxyethyl-2-phenylpyrimidin-6(1H)-one-5-carboxylate (93.00 g, 292.2 mmol) in 420.0 mL dry pyridine (0.70 M) was added lithium iodide (98.00 mL, 732.2 mmol) in one portion with stirring at room temperature, upon which an exotherm occurs. The resulting light brown suspension was heated to reflux for 2 hours. The dark brown reaction was allowed to cool to room temperature and the volatiles were removed under reduced pressure. The resulting oil was diluted with 1 N HCl (500 mL). The aqueous solution was extracted with dichloromethane/methanol (4:1, 4 x 250 mL). The combined organic solutions were washed with 6 N HCl (2 x 250 mL), dried (MgSO₄), filtered and concentrated. The crude product was purified by crystallization (ethyl acetate/hexane) to give pure 1-(2,2-dimethoxyethyl-2-phenylpyrimidin-6(1H)-one-5-carboxylate (EX-1B) in 63 % yield as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 12.99 (s, 1H), 8.97 (s, 1H), 7.63-7.51 (m, 5H), 4.78 (dd, *J* = 4.3, 5.5 Hz, 1H), 4.28 (d, *J* = 5.4 Hz, 2H), 3.30 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 165.1, 164.1, 159.1, 133.6, 131.5, 129.1, 129.0, 112.6, 101.0, 55.8, 49.2; HRMS (ES) calcd for C₁₅H₁₇N₂O₅ 305.1137, found 305.1113.

(EX-1C) A suspension of 1-(2,2-dimethoxyethyl-2-phenylpyrimidin-6(1H)-one-5-carboxylate (65.93 g, 216.67 mmol) in 800 mL 1,4-dioxane (0.27 M) was added triethylamine (50.0 mL, 358.7 mmol) followed by diphenylphosphoryl azide (51.40 mL, 238.5 mmol) in one portion at room temperature. The resulting solution was slowly heated to reflux for 2 hours. The reaction mixture was then added benzyl alcohol (45.00 mL, 434.8 mmol) and refluxing was maintained for approximately 14 hours. The black solution was allowed to cool to room temperature, and the volatiles were removed under vacuum. The resulting residue was diluted with ethyl acetate (1.5 L). The organic solution was washed with saturated NH₄Cl (2 x 500 mL), 1 N NaOH (1 x 500 mL), and brine (1 x 500 mL). The organic solution was dried (MgSO₄), filtered and concentrated to give the crude product. Purification by MPLC(15%-30% ethyl acetate/hexane) afforded pure [5-[(benzyloxycarbonyl)amino]-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetaldehyde dimethyl acetal (EX-1C) as light brown solid in 46% yield: ¹H NMR (400 MHz, CDCl₃) δ 8.72 (br s, 1H), 7.53-7.32 (m, 11H), 5.20 (s, 2H), 4.68 (t, *J* = 5.6 Hz, 1H), 4.12 (d, *J* = 5.6 Hz, 2H),

3.22 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.3, 153.7, 153.2, 135.9, 134.9, 134.7, 130.1, 129.1, 128.9, 128.8, 128.71, 128.66, 128.4, 125.1, 101.3, 67.7, 55.4, 48.6; HRMS (EI) calcd for $\text{C}_{22}\text{H}_{24}\text{N}_3\text{O}_5$ 410.1716, found 410.1741.

(EX-1D) A solution of [5-[(benzyloxycarbonyl)amino]-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetaldehyde dimethyl acetal (17.24 g, 42.11 mmol) in 103.0 mL tetrahydrofuran was added 35.0 mL 1 N HCl. The resulting biphasic mixture was allowed to heated to reflux for 12 hours. The reaction mixture was allowed to cool to room temperature and the volatiles were removed under vacuum. The resulting residue was diluted with water (200 mL) and the pH was adjusted to 7 by addition of solid NaHCO_3 . The resulting emulsion was extracted with dichloromethane (4 x 150 mL). The combined organic solutions were washed with water (1 x 200 mL), dried (MgSO_4), filtered, and concentrated to give 15.74 g crude [5-[(benzyloxycarbonyl)amino]-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetaldehyde.

A solution of crude [5-[(benzyloxycarbonyl)amino]-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetaldehyde (15.30 g, 42.11 mmol) in 198.0 mL of tetrahydrofuran, t-butyl alcohol, and 2-methyl-2-butene (1:1:1.3, 0.21 M) was cooled to 0°C . The solution was then slowly added a solution of sodium chlorite (29.94 g, 331.1 mmol) and sodium dihydrogenphosphate monohydrate (35.42 g, 256.7 mmol) in 102.0 mL of water (3.2 M based on sodium chlorite). The resulting gold colored, biphasic solution was stirred for 10 minutes and the cold bath was removed. The reaction was stirred for 1 hour at room temperature. The volatiles were removed under reduced pressure. The resulting solution was diluted with water (200 mL) and the pH was adjusted to 3 by addition of sat NaHCO_3 and 1 N HCl. The aqueous solution was extracted by tetrahydrofuran, dichloromethane (1:2, 4 x 180 mL). The combined organic solutions were dried (MgSO_4), filtered, and concentrated to give the crude product. Purification by trituration with ethyl ether gave an 88% yield of [5-[(benzyloxycarbonyl)amino]-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetic acid as a white solid: ^1H NMR (300 MHz, *d*-DMSO) δ 13.34 (br s, 1H), 9.03 (s, 1H), 7.57-7.34 (m, 10H), 5.23 (s, 2H), 4.56 (s, 2H); ^{13}C NMR (75 MHz, *d*-DMSO) δ 169.4, 158.0, 154.6, 154.3, 137.1, 134.8, 130.9, 129.4, 129.1, 128.78, 128.72, 128.50, 125.5, 67.0, 48.8; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_5$ 380.1246, found 380.1246.

(EX-1E) A suspension of [5-[(benzyloxycarbonyl)amino]-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetic acid (5.2503 g, 13.84 mmol) in 70.0 mL chloroform (0.2 M) was cooled in an ice bath to approximately 0°C. The cold suspension was then added oxalyl chloride (6.00 mL, 68.78 mmol) drop wise via syringe. After vigorous gas evolution, a golden homogeneous solution resulted. After stirring for 5 minutes, the cold bath was removed and the solution was stirred for an additional 2 hours at room temperature. The solvent was removed under reduced pressure and placed on the high vacuum system to remove residual solvents for 10 minutes. The resulting yellow solid was diluted with 70.0 mL chloroform (0.2 M) and added pyridine (1.70 mL, 21.02 mmol) and 2-methyl-2-propanol (3.50 ml, 36.60 mmol). The resulting tan colored solution was stirred for 1 hour at room temperature, and then heated to reflux for 12 hours. The reaction mixture was cooled to room temperature and diluted with chloroform (300 mL). The organic solution was washed with water (1 x 100 mL), saturated NaHCO₃ (1 x 100 mL), and brine (1 x 100 mL). The organic solution was dried (MgSO₄), filtered and concentrated. The crude reaction was purified by MPLC (25% ethyl acetate/hexanes) to give the product in 49% yield: ¹H NMR (300 MHz, CDCl₃) δ 8.81 (br s, 1H), 7.57-7.38 (m, 11H), 5.27 (s, 2H), 4.57 (s, 2H), 1.47 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 166.4, 158.0, 153.2, 135.9, 135.0, 134.4, 130.6, 129.1, 128.9, 128.7, 128.5, 128.4, 125.4, 83.4, 67.7, 49.1, 28.2; HRMS (EI) calcd for C₂₄H₂₆N₃O₅ 436.1872, found 436.1876.

(EX-1F) A solution of [5-amino-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetic acid *t*-butyl ester (1.8647 g, 4.282 mmol) in 21.0 mL methanol (0.2 M) was added 211.3 mg 10% Pd/C in one portion. The resulting mixture was stirred under an atmosphere of hydrogen gas (balloon) at room temperature for approximately 16 hours. The crude reaction mixture was filtered through a pad of Celite 545 and the solvent was removed under reduced pressure. The crude product was triturated from ethyl ether to give pure product [5-amino-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetic acid *t*-butyl ester (EX-1F) in 99% yield: ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.39 (m, 6H), 4.48 (s, 2H), 4.06 (br s, 2H), 1.39 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 158.6, 149.3, 134.9, 132.9, 130.0, 128.9, 128.5, 127.7, 82.9, 48.7, 28.1; HRMS (EI) calcd for C₁₆H₂₀N₃O₃ 302.1505, found 302.1491.

(EX-1G) A solution of [5-amino-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetic acid *t*-butyl ester (1.0300 g, 3.418 mmol) in 5.5 mL tetrahydrofuran and 2.0 mL dimethylformamide (0.45 M) was added N-methylmorpholine (1.20 mL, 10.91 mmol) in one portion. The solution was cooled to 0°C in an ice bath. After stirring for 10 minutes, a solution of 718.2 mg *a*-toluenesulfonyl chloride (3.767 mmol) in 5.5 mL tetrahydrofuran (0.68 M) was added drop wise over a 5 minute period. The reaction mixture was stirred for 2 hours at 0°C. The reaction mixture was diluted with ethyl acetate (150 mL). The organic solution was washed with 1 N HCl (2 x 25 mL), saturated NaHCO₃ (2 x 25 mL), and brine (1 x 50 mL). The organic solution was dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting yellow solid was triturated with ethyl ether, filtered, and dried under vacuum to afford pure product (EX-1G) as a white solid in 74% yield: ¹H NMR (400 MHz, *d*-DMSO) δ 9.34 (s, 1H), 7.76 (s, 1H), 7.55-7.28 (m, 10H), 4.59 (s, 2H), 4.49 (s, 2H), 1.32 (s, 9H); ¹³C NMR (100 MHz, *d*-DMSO) δ 167.0, 158.8, 156.5, 142.1, 134.5, 131.7, 131.0, 130.1, 129.4, 129.0, 128.94, 128.58, 124.8, 83.0, 59.6, 49.2, 28.1; HRMS (EI) calcd for C₂₃H₂₆N₃O₅S 456.1593, found 456.1597.

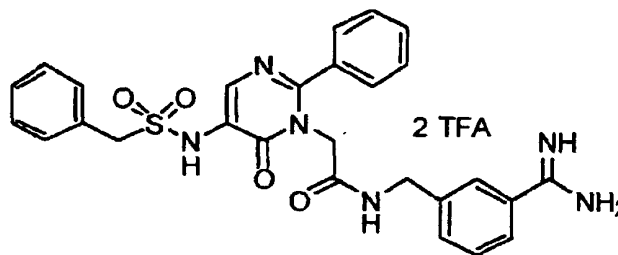
(EX-1H) A solution of (EX-1G) (1.0643 g, 2.336 mmol) in 9.0 mL 4M HCl in dioxane (0.1 M) was stirred for 12 hours at room temperature. The crude reaction was concentrated under reduced pressure. The resulting residue was triturated with ethyl ether to afford pure product (EX-1H) in 87% yield as a white solid: ¹H NMR (400 MHz, *d*-DMSO) δ 9.32 (s, 1H), 7.74 (s, 1H), 7.51-7.30 (m, 10H), 4.58 (s, 2H), 4.48 (s, 2H); ¹³C NMR (100 MHz, *d*-DMSO) δ 169.2, 158.7, 156.6, 141.9, 134.5, 131.7, 131.0, 130.1, 129.4, 129.0, 128.90, 128.56, 124.8, 59.6, 48.9; HRMS (EI) calcd for C₁₉H₁₈N₃O₅S 400.0967, found 400.0959.

(EX-1I) A solution of acid (EX-1H) (406.8 mg, 1.018 mmol) in 10.0 mL dimethylformamide (0.10 M) was added N,N-diisopropylethylamine (0.900 mL, 5.167 mmol), N-hydroxybenzotriazole (167.7 mg, 1.241 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (236.1 mg, 1.232 mmol). The resulting mixture was allowed to stir for 30 minutes at room temperature after which the mixture had become homogeneous. The reaction mixture was then added 4-(Cbz-amidino)benzylamine (324.6 mg, 1.126 mmol) in

one portion at room temperature. The resulting mixture was then allowed to stir for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL). The organic solution was washed with 5% citric acid (1 x 25 mL), saturated NaHCO₃ (1 x 25 mL), and brine (1 x 25 mL). The organic solution was dried (MgSO₄),
 5 filtered and concentrated. The crude reaction mixture was purified trituration with ethyl ether to afford pure product (EX-1I) in as a white solid: ¹H NMR (300 MHz, *d*-DMSO) δ 9.36-9.18 (br m, 3H), 8.82-8.78 (m, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.84, (s, 1H), 7.56-7.32 (m, 16H), 5.15 (s, 2H). 4.65 (s, 2H), 4.58 (s, 2H), 4.40 (d, *J* = 5.4 Hz, 2H); HRMS (EI) calcd for C₃₅H₃₃N₆O₆S₂ 665.2182,
 10 found 665.2177.

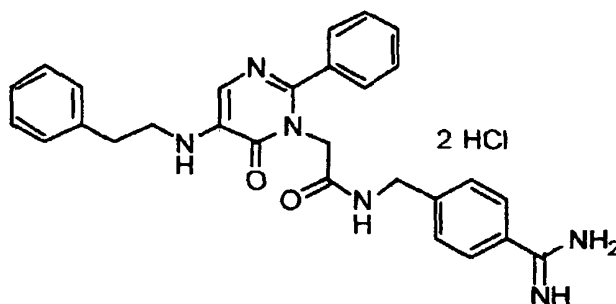
A solution of Cbz-amidine (EX-1I) (237.7 mg, 357.6 mmol) in 3.5 mL methanol and 4 M HCl in dioxane (4:1, 0.1 M) was added 42.1 mg 10% Pd/C in one portion. The resulting mixture was stirred under an atmosphere of hydrogen gas (balloon) at room temperature for approximately 16 hours. The crude reaction
 15 mixture was filtered through a pad of Celite 545 and the solvent was removed under reduced pressure. Purification of the crude product by HPLC (gradient, 5%-95% acetonitrile/water with 0.1% trifluoroacetic acid) afforded pure product as a white solid: ¹H NMR (300 MHz, *d*-DMSO) δ 9.31-9.28 (m, 4H), 8.88 (br s, 1H), 7.81-7.77 (m, 3H), 7.60-7.54 (m, 5H), 7.43-7.37 (m, 7H), 4.65 (s, 2H), 4.58 (s, 2H), 4.42-4.41 (m, 2H); HRMS (EI) calcd for C₂₇H₂₇O₄S 531.1815, found 531.1794.
 20

Example 2



25 By following the method of **Example 1**, the title compound was prepared: ¹H NMR (300 MHz, *d*-DMSO) δ 9.40-9.33 (m, 4H), 8.86 (s, 1H), 7.82 (s, 2H), 7.72-7.37 (m, 15H), 4.65-4.59 (m, 4H), 4.41-4.40 (m, 2H); HRMS (EI) calcd for C₂₇H₂₇N₆O₄S 531.1815, found 531.1794.

Example 3

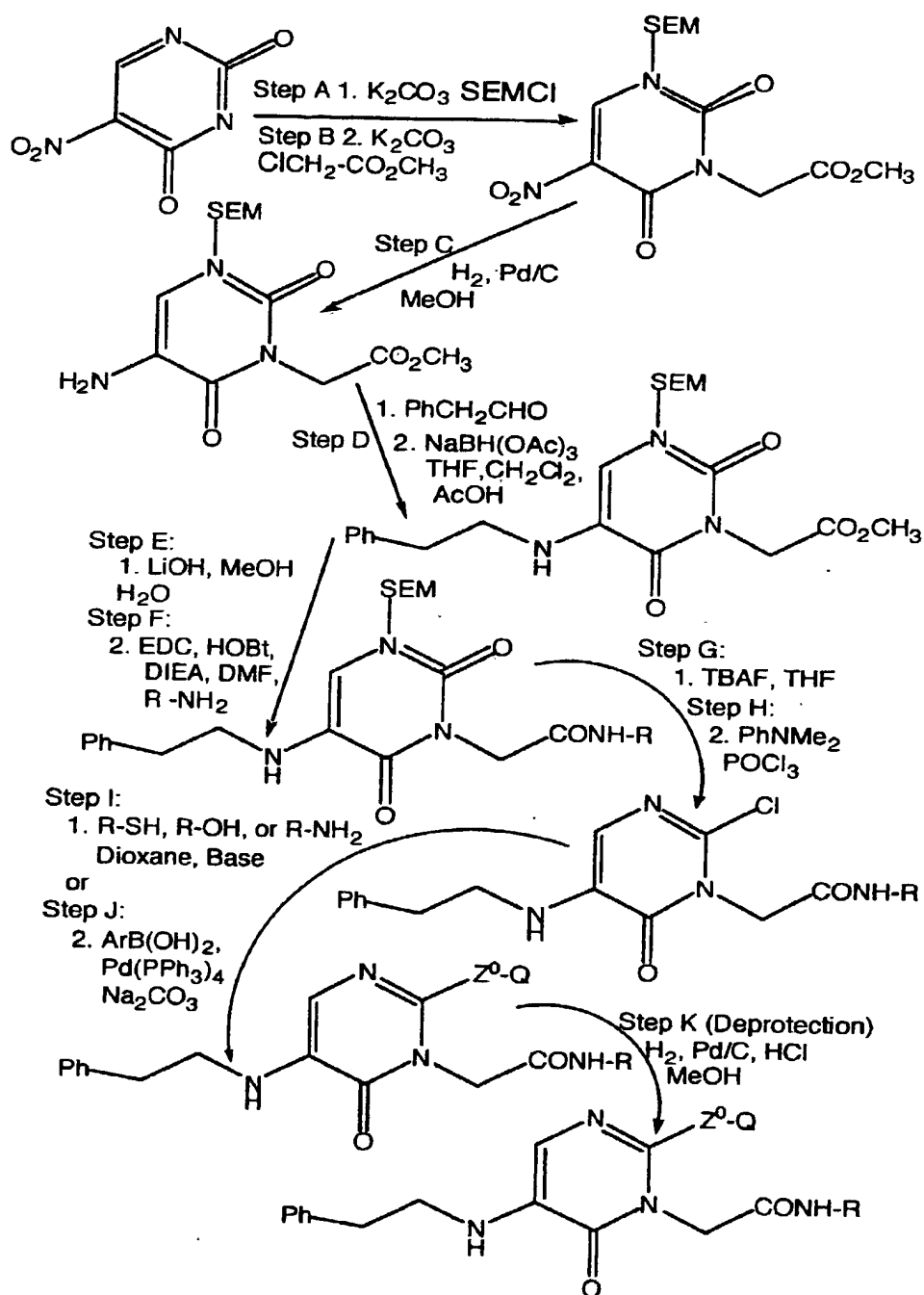


- (EX-3A) A solution of [5-amino-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetic acid *t*-butyl ester (EX-1F) (613.7 mg, 2.037 mmol) in 7.0 mL tetrahydrofuran and dichloromethane (1:1, 0.3 M) was added 25.0 mL acetic acid and phenylacetaldehyde (0.475 mL, 4.060 mmol). The solution was cooled to 0°C in an ice bath and added sodium triacetoxyborohydride (1.9131 g, 9.027 mmol) in one portion. After stirring for 5 minutes, the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 2 hours. The reaction was quenched by the addition of 1 N NaOH (5 mL), and the mixture was stirred for 5 minutes. The reaction mixture was diluted 0.5 N NaOH (100 mL). The aqueous solution was extracted with ethyl acetate (3 x 25 mL). The combined organic solutions were washed with 0.5 N NaOH (1 x 25 mL) and brine (1 x 25 mL). The solution was dried (MgSO₄), filtered and concentrated under reduced pressure.
- Purification by MPLC (25% ethyl acetate/hexanes) afforded EX-3A as a yellow oil in 74% yield: ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.40 (m, 4H), 7.31-7.26 (m, 2H), 7.23-7.16 (m, 5H), 4.70 (br s, 1H), 4.49 (s, 2H), 3.38-3.34 (m, 2H), 2.96-2.92 (m, 2H), 1.40 (s, 9H); HRMS (EI) calcd for C₂₄H₂₈N₃O₃ 406.2131, found 406-2125.
- A solution of EX-3A (521.3 mg, 1.286 mmol) in 13.0 mL 4M HCl in dioxane (0.1 M) was stirred for 12 hours at room temperature. The crude reaction was concentrated under reduced pressure. The resulting residue was triturated with ethyl ether to afford pure product EX-3B in quantitative yield as a yellow solid: ¹H NMR (300 MHz, *d*-DMSO) δ 7.66-7.57 (m, 5H), 7.33-7.23 (m, 6H), 4.57 (s, 2H), 3.44-3.35 (m, 2H), 2.97-2.92 (m, 2H); ¹³C NMR (75 MHz, *d*-DMSO) δ 168.8, 157.0, 148.0, 139.9, 135.0, 132.2, 129.69, 129.48, 129.07, 126.9, 48.8, 44.5, 34.5; HRMS (EI) calcd for C₂₀H₂₀N₃O₃ 350.1505, found 350.1520.

A solution of **EX-3B** (497.8 mg, 1.290 mmol) in 13.0 mL dimethylformamide (0.10 M) was added N,N-diisopropylethylamine (1.800 mL, 10.33 mmol), N-hydroxybenzotriazole (212.8 mg, 1.575 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (302.5 mg, 1.578 mmol). The resulting mixture was allowed to stir for 30 minutes at room temperature after which the mixture had become homogeneous. The reaction mixture was then added 4-(Cbz-amidino)benzylamine (410.9 mg, 1.425 mmol) in one portion at room temperature. The resulting mixture was then allowed to stir for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL). The organic solution was washed with 5% citric acid (1 x 25 mL), saturated NaHCO₃ (1 x 25 mL), and brine (1 x 25 mL). The organic solution was dried (MgSO₄), filtered and concentrated. The crude reaction mixture was purified trituration with ethyl ether to afford pure product **EX-3C** in as a white solid: ¹H NMR (400 MHz, *d*-DMSO) δ 9.08 (br s, 2 H), 8.62 (t, *J* = 5.8 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.44-7.15 (m, 17H), 5.35 (t, *J* = 5.9 Hz, 1H), 5.07 (s, 2H), 4.44 (s, 2H), 4.29 (d, *J* = 5.4 Hz, 2H), 3.31-3.26 (m, 2H), 2.88-2.85 (m, 2H); HRMS (EI) calcd for C₃₆H₃₃N₆O₄ 615.2720, found 615.2688.

A solution of **EX-3C** (222.6 mg, 362.1 mmol) in 4.0 mL methanol and 4 M HCl in dioxane (3:1, 0.1 M) was added 53.0 mg 10% Pd/C in one portion. The resulting mixture was stirred under an atmosphere of hydrogen gas (balloon) at room temperature for approximately 16 hours. The crude reaction mixture was filtered through a pad of Celite 545 and the solvent was removed under reduced pressure. Purification of the crude product by trituration from ethyl ether afforded pure product as a yellow solid: ¹H NMR (300 MHz, *d*-DMSO) δ 9.62-9.30 (br m, 5H), 7.88 (br m, 2H), 7.58-6.86 (br m, 15H), 4.59 (br s, 2H), 4.36 (br s, 2H), 3.38 (br s, 2H), 2.91 (br s, 2H); HRMS (EI) calcd for C₂₈H₂₉N₆O₂ 481.2352, found 481.2348.

Pyrimidinones having, for example, a directly bonded 2-aryl, 2-heteroaryl, or 2-heteroatom linking/bonding an organic group through the heteroatom to the pyrimidinone ring can be prepared using **Scheme 6** and **Scheme 7** below. The heteroatom is typically a sulfur, nitrogen, oxygen, or another suitable heteroatom. Use of the general procedure in **Scheme 6** to prepare specific heteroatom substituted pyrimidinones is disclosed in **Examples 4** and **5**.

Scheme 6. Preparation of 2-Substituted Pyrimidinones

temperature for 2 hours. The reaction is quenched by the addition of 1 N NaOH, and the mixture is stirred for 5 minutes. Typical aqueous work up, followed by chromatographic purification provides pure product **EX-4D**.

EX-4E) To a solution of 1-SEM-3-methoxycarbonylmethyl-5-(2-phenylethyl)amino-2,4(1H,3H)pyrimidinedione (**EX-4D**) in tetrahydrofuran and methanol (1:1, 0.2 M) is added 1 equivalent of lithium hydroxide in water. After the reaction is complete, the volatiles are removed under reduced pressure. The remaining aqueous solution is cooled in an ice bath and acidified to a pH of 1 with 1.0 N HCl. Extraction with organic solvent and removal of the solvent under reduced pressure gives pure product **EX-4E**.

EX-4F) To a solution of 1-SEM-3-methylenecarboxy-5-(2-phenylethyl)amino-2,4(1H,3H)pyrimidinedione dimethylformamide (0.1 M) are added 5 equivalents of N,N-diisopropylethylamine, 1 equivalent of N-hydroxybenzotriazole, and 1 equivalent of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. The resulting mixture is stirred for 30 minutes. The reaction mixture is then treated with 1 equivalent of the appropriate amine and allowed to stir over night. Typical aqueous work up followed by chromatographic purification gives pure product **EX-4F**.

EX-4G) To a solution of 1-SEM-3-methylenecarbamide-5-(2-phenylethyl)amino-2,4(1H,3H)pyrimidinedione in tetrahydrofuran (0.3M) is added 2 equivalents of tetrabutylammonium fluoride in tetrahydrofuran. The resulting solution is refluxed for several hours. Typical aqueous work up is followed by chromatographic purification to give pure product **EX-4G**.

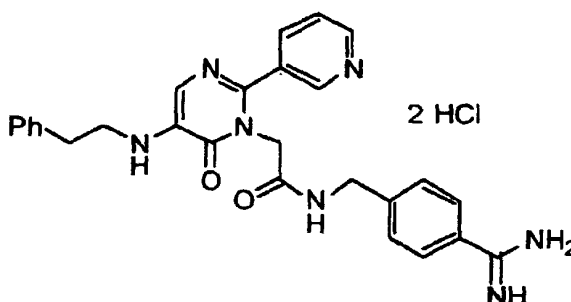
EX-4H) To a solution of 3-methylenecarboxamide-5-(2-phenylethyl)amino-2,4(1H,3H)pyrimidinedione (**EX-4G**) in N,N-dimethylaniline (0.3M) is added 1 equivalent of phosphorus oxychloride. The resulting solution is refluxed for several hours. Typical aqueous work up is followed by chromatographic purification to give pure product **EX-4H**.

EX-4I) To a solution of 2-chloro-3-methylenecarboxamide-5-(2-phenylethyl)amino-2,4(1H,3H)pyrimidinedione (**EX-4H**) in dioxane (0.3M) is added 2 equivalents of phenylthiol. The resulting solution is refluxed for several hours. Typical aqueous work up is followed by chromatographic purification to give pure product **EX-4I**.

A solution of 2-thiophenyl-3-methylenecarboxamide-5-(2-phenylethyl)amino-2,4(1H,3H)pyrimidinedione (**EX-4I**) in methanol and 4M

HCl dioxane (3:1, 0.1 M) is degassed with hydrogen gas. To the solution is then added 5% Pd/C which is stirred under an atmosphere of hydrogen at room temperature for 24 hours. The crude reaction is filtered through a pad of Celite 545 and concentrated under reduced pressure. Purification by column chromatography gives pure product.

Example 5



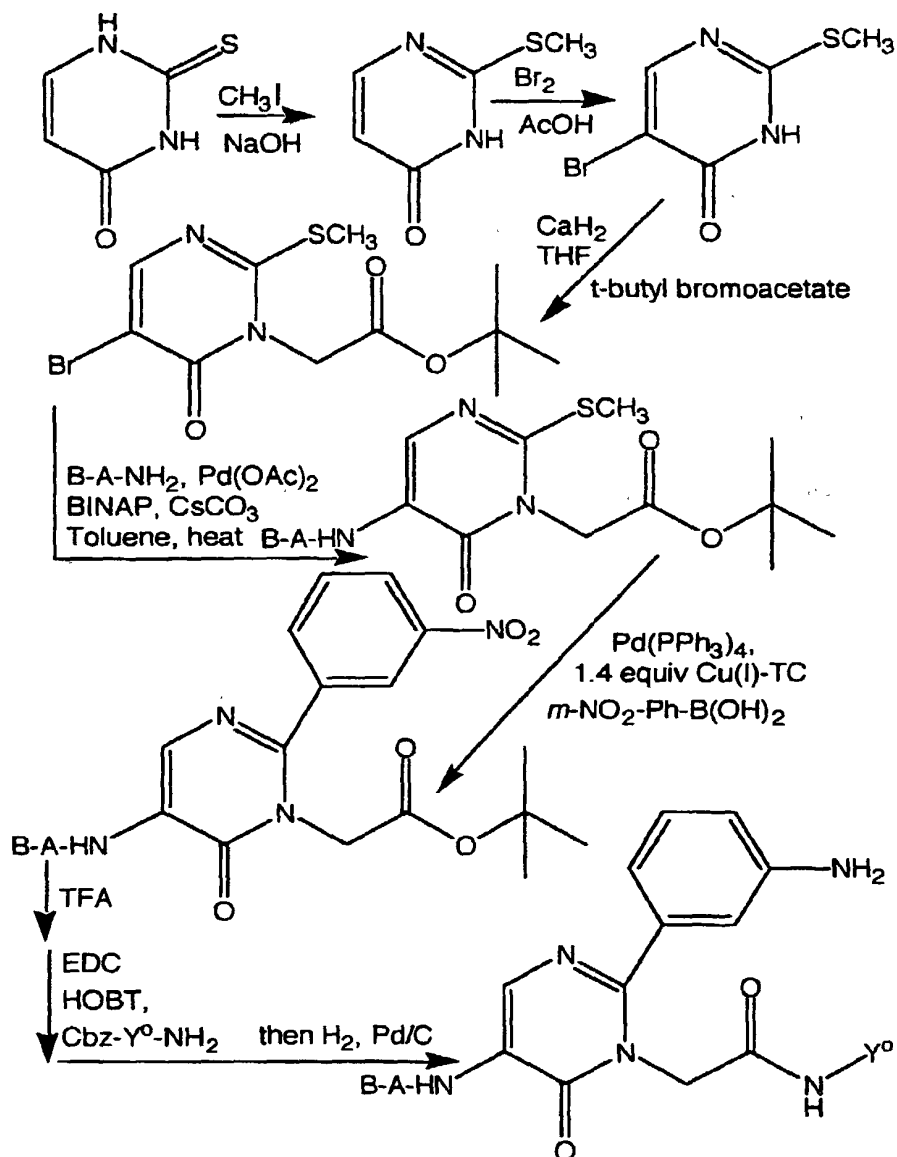
EX-5A) To a degassed solution of 2-chloro-3-methylenecarboxamide-5-(2-phenylethyl)amino-2,4(1H,3H)pyrimidin-6(1H)-one and 1 equivalent of 3-pyridineboronic acid in 1-propanol (0.5M) is added 1.2 equivalents of 2.0 M sodium carbonate followed by 1 mol % of tetrakis(triphenylphosphine)palladium. The resulting mixture is heated to reflux for several hours. After cooling to room temperature, typical aqueous work up is followed by chromatographic purification to give pure product **EX-5A**.

A solution of 2-(3-pyridinyl)-3-methylenecarboxamide-5-(2-phenylethyl)amino-2,4(1H,3H)pyrimidin-6(1H)-one (**EX-5A**) in methanol and 4M HCl dioxane (3:1, 0.1 M) is degassed with hydrogen gas. To the solution is then added 5% Pd/C, and the solution is stirred under an atmosphere of hydrogen at room temperature for 24 hours. The crude reaction is filtered through a pad of Celite 545 and concentrated under reduced pressure. Purification by column chromatography gives pure product.

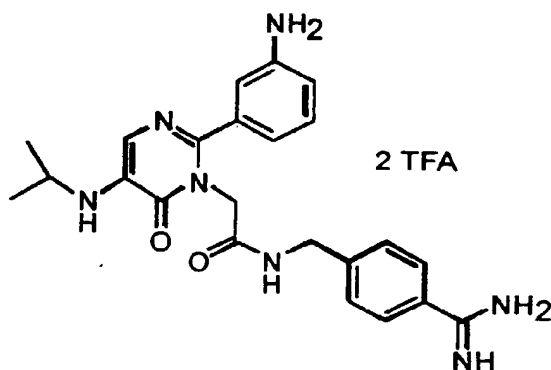
Pyrimidinones having, for example, a directly bonded 2-aryl, 2-heteroaryl, or 2-heteroatom linking/bonding an organic group through the heteroatom to the pyrimidinone ring can also be prepared using **Scheme 7** below. In this reaction scheme, the aryl is introduced by forming a carbon-carbon bond. Heteroatom suitable for forming heterolinked aryl pyrimidinones include sulfur, nitrogen, oxygen, or another suitable heteroatom. Use of the general procedure in

Scheme 7 to prepare specific heteroatom substituted pyrimidinones is disclosed in **Examples 6** and **7**.

Scheme 7: Alternate Pyrimidinone Synthesis



Example 6



(EX-6A) 2-Thiouracil (66.7 g, 520.5 mmol) was dissolved in a sodium hydroxide solution (41.6 g of solid NaOH in 365 mL of water). The mixture was then treated with methyl iodide (37 mL, 583 mmol), and the resulting reaction mixture was allowed to stir for 16 h at room temperature. The solution was then acidified with glacial acetic acid (30 mL). The white precipitate was collected by suction filtration, and the solid was washed several times with cold water and dried to afford 74 g of EX-6A as a white crystalline solid in quantitative yield.

(EX-6B) A solution of EX-6A (74.0 g, 520.5 mmol) in glacial acetic acid (2275 mL) was cooled to 0 °C with an ice bath and treated with Br₂. The reaction mixture was allowed to warm to room temperature, and to stir for 16 h. A yellow precipitate formed which was filtered and washed with ether three times. 97.2 g of EX-6B was isolated in 62% yield.

(EX-6C) A mixture of calcium hydride in THF was cooled to 0 °C and treated with neat EX-6B followed by neat *t*-butyl bromoacetate. The reaction mixture was allowed to stir at 0 °C for 1h. The reaction mixture was then allowed to stir for 2h after the mixture was allowed to warm to room temperature. The reaction mixture was heated to reflux temperature for 16 h. After the reaction mixture was cooled to room temperature, the mixture was slowly poured into a 1 L ice water slurry. The quenched mixture was extracted with dichloromethane (3 x 500mL). The organic layers were combined and washed with water and brine. After the organic layer was dried over MgSO₄ and filtered, the volatile components were removed *in vacuo* to afford 28.81 g (90%) of EX-6C as an off white solid as a mixture of N-alkylated and O-alkylated isomers (9:1). N-alkylated isomer: ¹H NMR (300 MHz, CDCl₃) δ 8.07 (s, 1H), 4.75 (s, 2H), 2.57 (s, 3H), 1.47 (s,

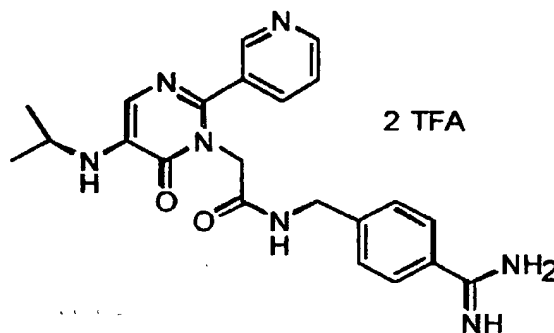
WO 00/69832

PCT/US00/09806

(d), 121.8 (d), 67.4 (t), 49.9 (t), 44.1 (d), 43.2 (t), 22.4 (q); HRMS (ESI) calcd for $C_{31}H_{32}N_7O_6$ $[M + H]^+$: 598.2463, found 598.2414.

Prepared from **EX-6G** according to the method described for SC-81703 to afford the product: 1H NMR (300 MHz, CD_3OD) δ 9.25 (bs, 1 H), 8.97 (m, 1 H), 8.78 (bs, 1 H), 7.93 - 7.14 (complex m, 9 H), 4.77 (s, 2 H), 4.51 (s, 3 H), 3.66 (m, 1 H), 1.30 (d, $J = 6.3$ Hz, 6 H); HRMS (ESI) calcd for $C_{23}H_{28}N_7O_2$ $[M + H]^+$ = 598 of free base 434.2304, found 434.2318.

Example 7



(**EX-7A**) Prepared from **EX-6D** using the same procedure described for **EX-6E** with the only exception that Cs_2CO_3 base was used. As such, **EX-6D** (213 mg, 0.68 mmol), pyridine-3-boronic acid 1,3-propanediol cyclic ester (166 mg, 1.02 mmol) and Cs_2CO_3 (771 mg, 2.37 mmol) afforded 143 mg of **EX-7A** (61 % yield) after flash chromatography (Merck 230-400 mesh SiO_2 , 2 % MeOH in $CHCl_3$) as a slightly yellow glass: 1H NMR (300 MHz, $CDCl_3$) δ 8.79 - 8.66 (m, 2 H), 7.90 - 7.26 (complex m, 3 H), 7.16 (s, 1 H), 4.53 (s, 2 H), 3.57 (septet, $J = 6.3$ Hz, 1 H), 1.44 (s, 9 H), 1.27 (d, $J = 6.3$ Hz, 6 H); HRMS (ESI) calcd for $C_{18}H_{25}N_4O_3$ $[M+H]^+$ = 345.1927, found 345.1928.

(**EX-7B**) Prepared from **EX-7A** (143 mg, 0.41 mmol) using the same procedure described for **EX-6F** to afford 212 mg (100 % yield) of **EX-7B** as a yellow foam: 1H NMR (300 MHz, $CDCl_3$) δ 8.72 - 8.64 (m, 2 H), 7.95 - 7.89 (m, 1 H), 7.62 - 7.52 (complex m, 2 H), 7.42 - 7.37 (m, 1 H), 7.20 (s, 1 H),

WO 00/69832

PCT/US00/09806

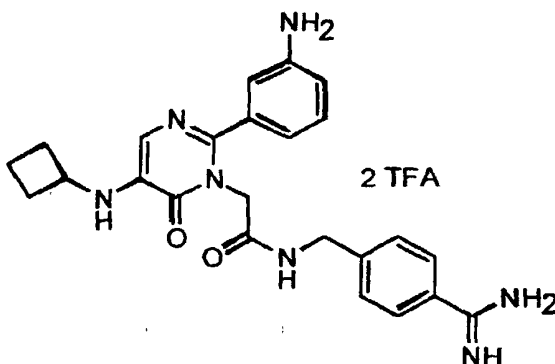
4.52 (s, 2 H), 3.57 (septet, $J = 6.3$ Hz, 1 H), 1.18 (d, $J = 6.3$ Hz, 6 H); HRMS (ESI) calcd for $C_{14}H_{17}N_4O_3$ $[M + H]^+$ 289.1301, found 289.1296.

(EX-7C) Prepared from EX-7B using the same procedure described for the CBZ-protected material to afford EX-7C; HRMS (ESI) calcd for

5 $C_{30}H_{32}N_7O_4$ $[M+H]^+ = 554.2516$, found 554.2523.

Prepared from EX-7C using the same procedure described for Example 6 to afford the product.

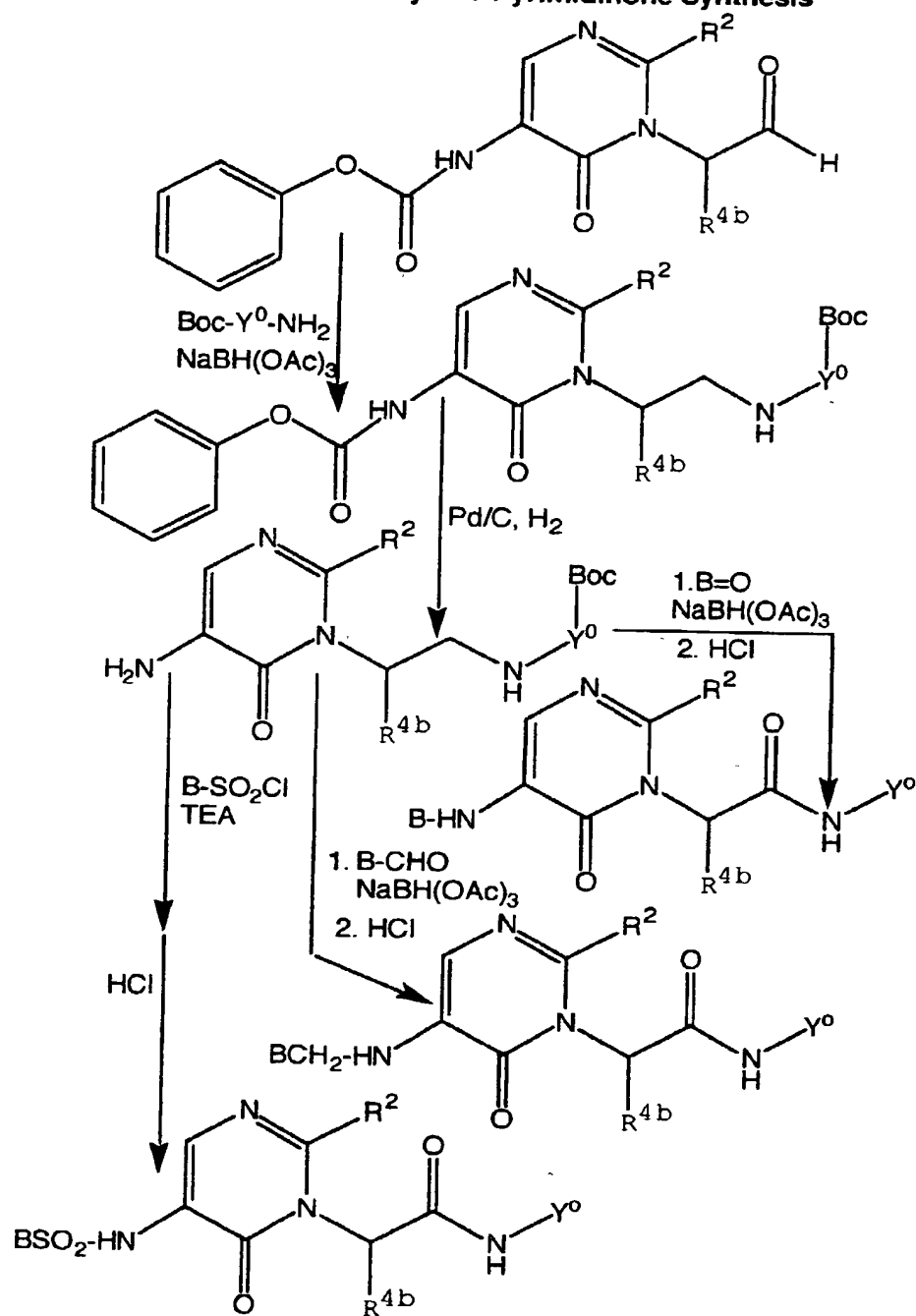
Example 8

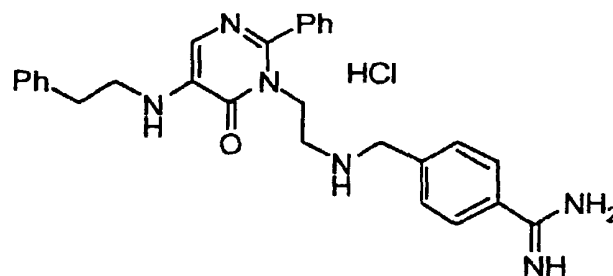


10 By following the method of Example 6, the title compound was prepared:
HRMS (ESI) calcd for $C_{24}H_{27}N_7O_2$ $[M+H]^+$ 446.2304, found 446.2309.

Methylene analogs of pyrimidinones wherein a methylene is present as a replacement for the carbonyl of the acetamide at the N-3 position of the pyrimidinone can be prepared using Scheme 8 "A General Methylene

15 Pyrimidinone Preparation" as detailed below along with the specific Example 9.

Scheme 8: General Methylene Pyrimidinone Synthesis

Example 9

EX-9A) To a solution of [[5-[(benzyloxycarbonyl)amino]-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetaldehyde in tetrahydrofuran and dichloromethane (1:1, 0.3 M) is added a catalytic amount of acetic acid and 1 equivalent of the appropriate amine. The solution is cooled to 0°C in an ice bath, and 1 equivalent sodium triacetoxyborohydride is added in one portion. After stirring for 5 minutes, the ice bath is removed, and the reaction mixture is allowed to stir at room temperature for 2 hours. The reaction is quenched by the addition of 1 N NaOH, and the mixture is stirred for 5 minutes. Typical aqueous work up is followed by chromatographic purification to provide pure product **EX-9A**.

EX-9B) To a solution of [5-[(benzyloxycarbonyl)amino]-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetamide (**EX-9A**) in methanol (0.2 M) is added 10% Pd/C in one portion. The resulting mixture is stirred under an atmosphere of hydrogen gas (balloon) at room temperature for approximately 16 hours. The crude reaction mixture is filtered through a pad of Celite 545, and the solvent is removed under reduced pressure. Trituration of the residue from ethyl ether gives pure product **EX-9B**.

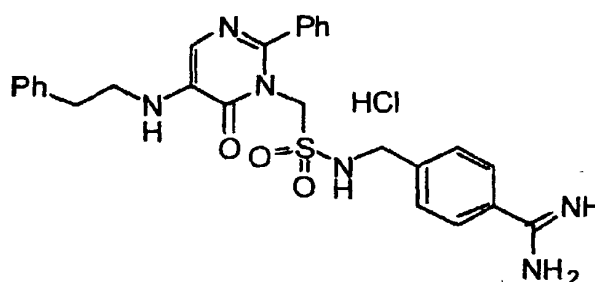
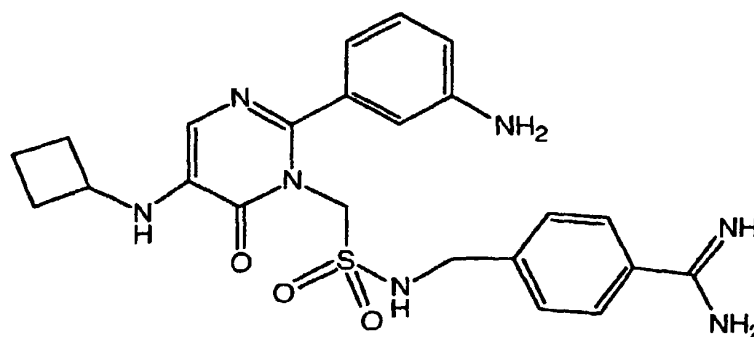
EX-9C) To a solution of [5-amino-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetamide (**EX-9B**) in tetrahydrofuran and dichloromethane (1:1, 0.3 M) is added a catalytic amount of acetic acid and 1 equivalent phenylacetaldehyde. The solution is cooled to 0°C in an ice bath, and 1 equivalent sodium triacetoxyborohydride is added in one portion. After stirring for 5 minutes, the ice bath is removed, and the reaction mixture is allowed to stir at room temperature for 2 hours. The reaction is quenched by the addition of 1 N NaOH, and the mixture is stirred for 5 minutes. Typical aqueous work up is followed by chromatographic purification to provide pure product **EX-9C**.

A solution of [5-(2-phenylethyl)amino-2-phenyl-6-oxo-1,6-dihydro-1-pyrimidinyl]acetamide in 4M HCl dioxane (0.2 M) is stirred for several hours.

After the reaction is complete, the volatiles are removed under reduced pressure. The residue is purified by trituration with ethyl ether to afford pure product **5**.

Sulfonyl analogs of pyrimidinones wherein a sulfonyl is present as a replacement for the carbonyl of the acetamide at the N-3 position of the pyrimidinone can be prepared using procedures generally based on those disclosed in **Schemes 1-5** by substituting an appropriate aminomethanesulfonamide of an N-Boc-amidino-protected amine in place of the 1,1-dimethoxyethylamine. For example, the N-(4-amidinobenzyl)2-aminomethanesulfonamide can be used. Using this approach, sulfonyl analogs in **Examples 10** and **11** can be prepared.

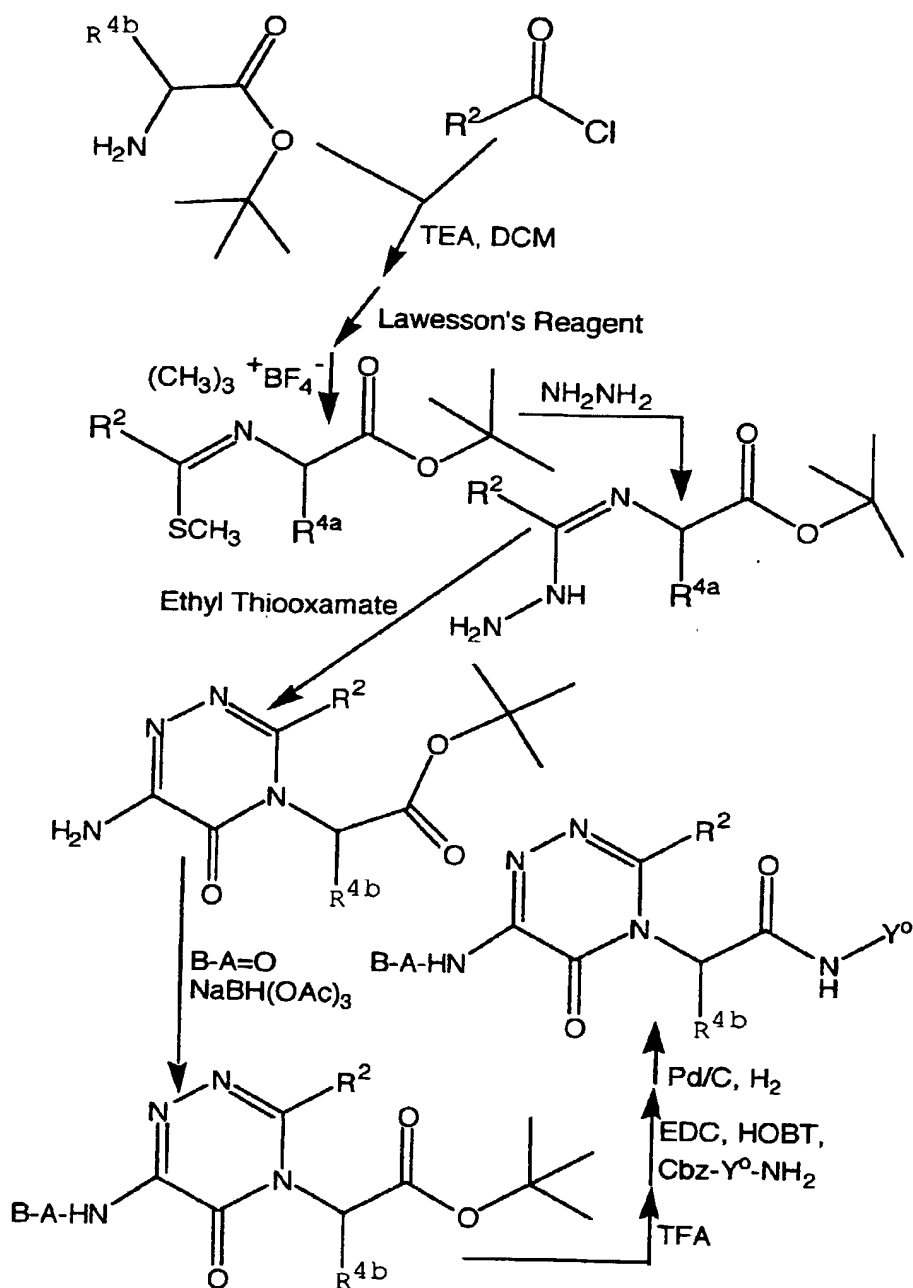
10

Example 10**Example 11**

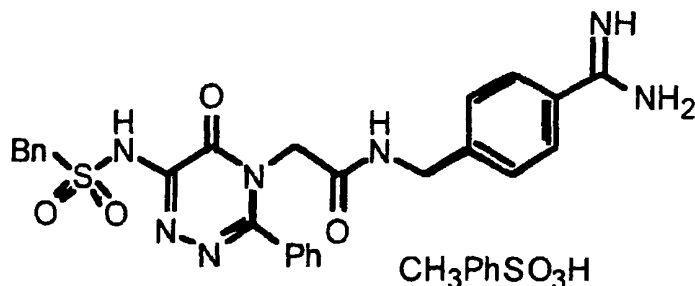
15

Triazinone analogs of pyrimidinones wherein a nitrogen is present as a replacement for the carbon at the 4-position of the pyrimidinone can be prepared using **Scheme 9** "A General 4-Aza Pyrimidinone Preparation" as detailed below along with the specific **Example 12**.

Scheme 9: General 4-AzaPyrimidinone Synthesis



Example 12



EX-12) A solution of glycine *t*-butyl ester hydrochloride (1 mmol) in dichloromethane is treated with benzoyl chloride (1 mmol) and triethyl amine (2 mmol). The reaction mixture is allowed to stir at room temperature for 16 h. The mixture is washed with water and extracted with dichloromethane. The combined organic layers are dried over $MgSO_4$. After removing the volatiles *in vacuo* pure product **EX-12A** is isolated.

EX-12B) A mixture of *N*-benzoylglycine *t*-butyl ester (1 mmol; **EX-12A**), Lawesson's reagent (0.5 mmol) and toluene are heated to 80 °C for 16h. The reaction mixture is concentrated under reduced pressure. Purification *via* column chromatography on silica gel gives pure product **EX-12B**.

EX-12C) A mixture of *N*-thiobenzoylglycine *t*-butyl ester (1 mmol; **EX-12B**) in dichloromethane is treated with trimethyloxonium tetrafluoroborate (1.1 mmol) at - 78 °C. After stirring the reaction mixture for 2 h, the mixture is washed with $NaHCO_3$ (aq) and extracted with dichloromethane. The combined organic layers are dried over $MgSO_4$ and filtered. After concentration of the volatile organic components, the desired product **EX-12C** is isolated.

EX-12D) A solution of *N*-thiomethylbenzylglycine *t*-butyl ester (1 mmol; **EX-12C**) in methanol is treated with hydrazine (1 mmol). The volatile materials are removed *in vacuo*, and the desired compound **EX-12D** is isolated without further purification.

EX-12E) A mixture of compound **EX-12D** (1 mmol) and ethyl thiooxamate (1 mmol) in methanol is heated to reflux temperature for 4 h. A precipitation of colorless crystals occurs, and the crystals of the desired product **EX-12E** are isolated by suction filtration.

A solution of compound **EX-12E** (1 mmol) and pyridine (5 mmol) in acetonitrile is treated with a solution of *p*-toluenesulfonyl chloride (3 mmol) in

acetonitrile. The reaction mixture is stirred at -10 °C to 0 °C for 3 h. A white precipitate forms after the reaction is complete. The crystals of the desired product **EX-12F** are isolated by suction filtration.

EX-12G) Trifluoroacetic acid is added to a mixture of compound **EX-12F** (1 mmol) in anisole at 0 °C. The reaction mixture is allowed to stir at 0 °C for 1 h. The reaction mixture is extracted with an organic solvent. Removal of the organic solvent under reduced pressure gives pure product **EX-12G**.

EX-12H) Compound **EX-12G** (1 mmol), EDC(1.3 mmol), and HOBT (1.3 mmol) are mixed in DMF, and the mixture is stirred at 20 °C for 15 minutes. To this mixture is added a solution of benzyl-[[[4-aminomethylphenyl]iminomethyl] amino]carbamate hydrogen chloride salt (1.3 mmol) and DIEA (1.3 mmol) in DMF. Typical aqueous work-up is followed by chromatographic purification to provide the desired product **EX-12H**.

Compound **EX-12H** (1 mmol), *p*-toluene sulfonic acid mono hydrate (1 mmol) and 10% Pd on activated carbon (0.1 mmol) are mixed with methanol. The mixture is stirred for 2 h under hydrogen atmosphere which is introduced and maintained through a rubber balloon. After filtering off the catalyst and removing the methanol, the desired product is isolated.

Formula (I) compounds of this invention possessing hydroxyl, thiol, and amine functional groups can be converted to a wide variety derivatives. Alternatively, derivatized Formula (I) compounds can be obtained by first derivatizing one or more intermediates in the processes of preparation before further transforming the derivatized intermediate to compounds of Formula (I). A hydroxyl group in the form of an alcohol or phenol can be readily converted to esters of carboxylic, sulfonic, carbamic, phosphonic, and phosphoric acids. Acylation to form a carboxylic acid ester is readily effected using a suitable acylating reagent such as an aliphatic acid anhydride or acid chloride. The corresponding aryl and heteroaryl acid anhydrides and acid chlorides can also be used. Such reactions are generally carried out using an amine catalyst such as pyridine in an inert solvent. Similarly, carbamic acid esters (urethanes) can be obtained by reacting a hydroxyl group with isocyanates and carbamoyl chlorides. Sulfonate, phosphonate, and phosphate esters can be prepared using the corresponding acid chloride and similar reagents. Compounds of Formula (I) that have at least one thiol group present can be converted to the corresponding thioesters derivatives analogous to those of alcohols and phenols using the same

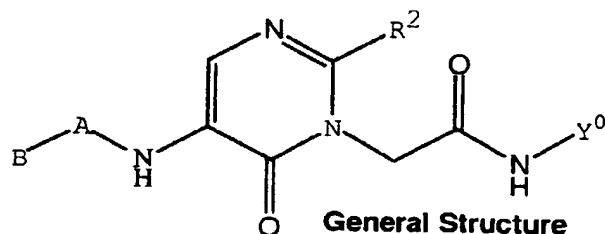
reagents and comparable reaction conditions. Compounds of Formula (I) that have at least one primary or secondary amine group present can be converted to the corresponding amide derivatives. Amides of carboxylic acids can be prepared using the appropriate acid chloride or anhydrides with reaction conditions analogous to those used with alcohols and phenols. Ureas of the corresponding primary or secondary amine can be prepared using isocyanates directly and carbamoyl chlorides in the presence of an acid scavenger such as triethylamine or pyridine. Sulfonamides can be prepared from the corresponding sulfonyl chloride in the presence of aqueous sodium hydroxide or a tertiary amine. Suitable procedures and methods for preparing these derivatives can be found in House's Modern Synthetic Reactions, W. A. Benjamin, Inc., Shriner, Fuson, and Curtin in The Systematic Identification of Organic Compounds, 5th Edition, John Wiley & Sons, and Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons. Reagents of a wide variety that can be used to derivatize hydroxyl, thiol, and amines of compounds of Formula (I) are available from commercial sources or the references cited above, which are incorporated herein by reference.

Formula (I) compounds of this invention possessing hydroxyl, thiol, and amine functional groups can be alkylated to a wide variety of derivatives. Alternatively, alkylated Formula (I) compounds can be obtained by first alkylating one or more intermediates in the processes of preparation before further transforming the alkylated intermediate to compounds of Formula (I). A hydroxyl group of compounds of Formula (I) can be readily converted to ethers. Alkylation to form an ether is readily effected using a suitable alkylating reagent such as an alkyl bromide, alkyl iodide or alkyl sulfonate. The corresponding aralkyl, heteroaralkyl, alkoxyalkyl, aralkoxyalkyl, and heteroaralkoxyalkyl bromides, iodides, and sulfonates can also be used. Such reactions are generally carried out using an alkoxide forming reagent such as sodium hydride, potassium t-butoxide, sodium amide, lithium amide, and n-butyl lithium using an inert polar solvent such as DMF, DMSO, THF, and similar, comparable solvents. amine catalyst such as pyridine in an inert solvent. Compounds of Formula (I) that have at least one thiol group present can be converted to the corresponding thioether derivatives analogous to those of alcohols and phenols using the same reagents and comparable reaction conditions. Compounds of Formula (I) that have at least one primary, secondary or tertiary amine group present can be converted to the corresponding secondary, tertiary or quaternary ammonium derivative. Quaternary

ammonium derivatives can be prepared using the appropriate bromides, iodides, and sulfonates analogous to those used with alcohols and phenols. Conditions involve reaction of the amine by warming it with the alkylating reagent with a stoichiometric amount of the amine (i.e., one equivalent with a tertiary amine, two
5 with a secondary, and three with a primary). With primary and secondary amines, two and one equivalents, respectively, of an acid scavenger are used concurrently. Secondary or tertiary amines can be prepared from the corresponding primary or secondary amine. A primary amine can be dialkylated by reductive amination using an aldehyde, such as formaldehyde, and sodium cyanoborohydride in the presence
10 of glacial acetic acid. A primary amine can be monoalkylated by first mono-protecting the amine with a readily cleaved protecting group, such as trifluoroacetyl. An alkylating agent, such as dimethylsulfate, in the presence of a non-nucleophilic base, such as Barton's base (2-*tert*-butyl-1,1,3,3-tetramethylguanidine), gives the monomethylated protected amine. Removal of the protecting group using aqueous
15 potassium hydroxide gives the desired monoalkylated amine. Additional suitable procedures and methods for preparing these derivatives can be found in House's Modern Synthetic Reactions, W. A. Benjamin, Inc., Shriner, Fuson, and Curtin in The Systematic Identification of Organic Compounds, 5th Edition, John Wiley & Sons, and Fieser and Fieser in Reagents for Organic Synthesis published by John
20 Wiley & Sons. Perfluoroalkyl derivatives can be prepared as described by DesMarteau in J. Chem. Soc. Chem. Commun. 2241 (1998). Reagents of a wide variety that can be used to derivatize hydroxyl, thiol, and amines of compounds of Formula (I) are available from commercial sources or the references cited above, which are incorporated herein by reference.

25 The results of the aforementioned synthetic approaches to the preparation pyrimidinones by derivatization of a nucleophilic substituent such as may be present in B, R¹, R² and Y⁰ are shown in Table 1 for the specific **Examples 13 through 19**. The specific examples recited below should be considered as being merely illustrative of the wide variety possible and not as
30 limiting to one of ordinary skill in the art.

Table 1. Structures of Pyrimidinones Prepared by
General Derivatization Procedures



Ex. No.	R ²	B-A-	Y ^O	MW (m/z+1)
13	phenyl	methoxyacetyl	4-amidinobenzyl	449.47
14	phenyl	4-methylbenzoyl	4-amidinobenzyl	495.54
15	phenyl	4-nitrobenzoyl	4-amidinobenzyl	526.52
16	phenyl	isobutyryl	4-amidinobenzyl	447.50
17	phenyl	2,4,6-trimethylbenzoyl	4-amidinobenzyl	523.60
18	phenyl	benzoyl	4-amidinobenzyl	481.52
19	phenyl	acetyl	4-amidobenzyl	419.45

5

Assays for Biological Activity

TF-VIIa Assay

In this assay 100 nM recombinant soluble tissue factor and 2nM recombinant human factor VIIa are added to a 96-well assay plate containing 0.4 mM of the substrate, N-Methylsulfonyl-D-phe-gly-arg-p-nitroaniline and either inhibitor or buffer (5 mM CaCl₂, 50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reaction, in a final volume of 100 ul is measured immediately at 405 nm to determine background absorbance. The plate is incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate is measured by monitoring the reaction at 405 nm for the release of p-nitroaniline. Percent inhibition of TF-VIIa activity is calculated from OD_{405nm} value from the experimental and control sample.

Xa Assay

0.3 nM human factor Xa and 0.15 mM N-α-Benzylloxycarbonyl-D-arginyl-L-glycyl-L-arginine-p-nitroaniline-dihydrochloride (S-2765) are added to a 96-well

assay plate containing either inhibitor or buffer (50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reaction, in a final volume of 100 μ l is measured immediately at 405 nm to determine background absorbance. The plate is incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate is measured by monitoring the reaction at 405 nm for the release of p-nitroaniline. Percent inhibition of Xa activity is calculated from OD_{405nm} value from the experimental and control sample.

Thrombin Assay

- 0.28 nM human thrombin and 0.06 mM H-D-Phenylalanyl-L-pipecolyl-L-arginine-p-nitroaniline dihydrochloride are added to a 96-well assay plate containing either inhibitor or buffer (50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reaction, in a final volume of 100 μ l is measured immediately at 405 nm to determine background absorbance. The plate is incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate is measured by monitoring the reaction at 405 nm for the release of p-nitroaniline. Percent inhibition of thrombin activity is calculated from OD_{405nm} value from the experimental and control sample.

Trypsin Assay

- 5 μ g/ml trypsin, type IX from porcine pancreas and 0.375 mM N- α -Benzoyl-L-arginine-p-nitroanilide (L-BAPNA) are added to a 96-well assay plate containing either inhibitor or buffer (50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reactions, in a final volume of 100 μ l are measured immediately at 405 nm to determine background absorbance. The plate is incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate is measured by monitoring the reaction at 405 nm for the release of p-nitroaniline. Percent inhibition of trypsin activity is calculated from OD_{405nm} value from the experimental and control sample.

- Recombinant soluble TF, consisting of amino acids 1-219 of the mature protein sequence was expressed in E. coli and purified using a Mono Q Sepharose FPLC. Recombinant human VIIa was purchased from American Diagnostica, Greenwich CT and chromogenic substrate N-Methylsulfonyl-D-phe-gly-arg-p-nitroaniline was prepared by American Peptide Company, Inc., Sunnyvale, CA. Factor Xa was obtained from Enzyme Research Laboratories, South Bend IN, thrombin from Calbiochem, La Jolla, CA, and trypsin and L-

WO 00/69832

PCT/US00/09806

BAPNA from Sigma, St. Louis MO. The chromogenic substrates S-2765 and S-2238 were purchased from Chromogenix, Sweden.

The biological activity of the compounds of **Examples 1 through 19** as determined by the bioassay procedures is summarized in the Table 2.

5

Table 2. Inhibitory Activity of Pyrimidinones toward Factor Xa, TF-VIIA, Thrombin II, and Trypsin II.

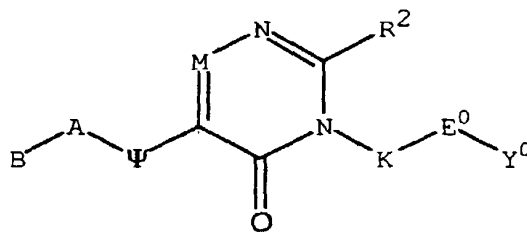
Example Number	TF-VIIA IC50 (uM)	Thrombin II IC50 (uM)	Factor Xa IC50 (uM)	Trypsin II IC50 (uM)
1	15.4	22.4	--	0.5
2	>30	>30	--	>30
3	1.0	1.0	--	0.6
4	--	--	--	--
5	--	--	--	--
6	0.05	43% @ 30 uM	33% @ 30 uM	<0.04
7	0.7	11.3	33% @ 30 uM	0.04
8	0.08	42% @ 30 uM	15% @ 30 uM	0.04
9	--	--	--	--
10	--	--	--	--
11	--	--	--	--
12	--	--	--	--
13	--	--	--	--
14	--	--	--	--
15	--	--	--	--
16	--	--	--	--
17	--	--	--	--
18	--	--	--	--
19	--	--	--	--

WO 00/69832

PCT/US00/09806

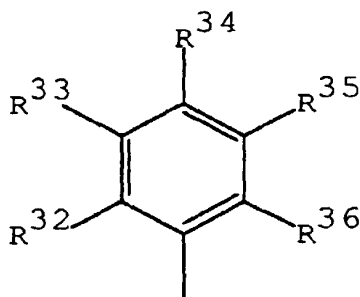
What we claim is:

1. A compound having the Formula:



or a pharmaceutically acceptable salt thereof, wherein;

5 B is the Formula:



$R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{32}, R^{33}, R^{34}, R^{35},$ and R^{36} are

independently selected from the group consisting of hydrido, acetamido,
haloacetamido, amidino, guanidino, alkylenedioxy, haloalkylthio,

10 alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, hydroxy, amino,
alkoxyamino, nitro, lower alkylamino, alkylthio, alkylthioalkyl, alkylsulfinyl,
alkylsulfonyl, alkylsulfonylalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl
amidosulfonyl, dialkyl amidosulfonyl, alkanoyl, haloalkanoyl, alkyl, alkenyl,
15 halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyalkyl,
aminoalkyl, haloalkoxyalkyl, carboxyalkyl, carboalkoxy, carboxy,
carboxamido, carboxamidoalkyl, and cyano;

$R^9, R^{10}, R^{11}, R^{12},$ and R^{13} are optionally selected from the group

consisting of heteroaryl and heterocyclyl with the proviso that $R^9, R^{10}, R^{11},$

20 $R^{12},$ and R^{13} are substituents for other than B;

R^{16} , R^{19} , R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently optionally

Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

5 B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2-C8 alkyl, C3-C8 alkylenyl, C3-C8 alkenyl, C3-C8 alkynyl, and C2-C8 haloalkyl, wherein each member of group B may be optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

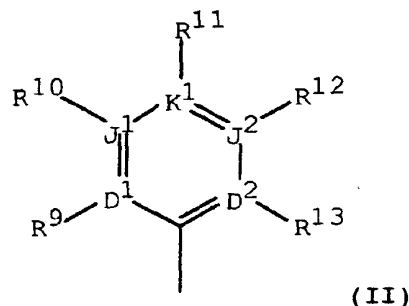
10 B is selected from the group consisting of C3-C12 cycloalkyl and C4-heterocyclyl, wherein each ring carbon may be optionally substituted with R^{33} , a ring carbon other than the ring carbon at the point of attachment of B to A may be optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbons and nitrogens
15 adjacent to the carbon at the point of attachment may be optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment may be substituted with R^{10} , a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment may be substituted with R^{12} , a ring carbon three atoms from the
20 point of attachment and adjacent to the R^{10} position may be substituted with R^{11} , a ring carbon three atoms from the point of attachment and adjacent to the R^{12} position may be substituted with R^{33} , and a ring carbon four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions may be substituted with R^{34} ;

- A is selected from the group consisting of single covalent bond,
 $(W^7)_{\pi}-(CH(R^{15}))_{pa}$ and $(CH(R^{15}))_{pa}-(W^7)_{\pi}$ wherein π is an integer
 selected from 0 through 1, pa is an integer selected from 0 through 6, and W^7
 is selected from the group consisting of O, S, C(O), $(R^7)NC(O)$, $(R^7)NC(S)$,
 5 and $N(R^7)$ with the proviso that no more than one of the group consisting of π
 and pa is 0 at the same time;
 R^7 is selected from the group consisting of hydrido, hydroxy, and
 alkyl;
 R^{15} is selected from the group consisting of hydrido, hydroxy, halo,
 10 alkyl, and haloalkyl;
 Ψ is selected from the group consisting of NH and NOH;
 M is selected from the group consisting of N and R^1-C ;
 R^1 is selected from the group consisting of hydrido, alkyl, alkenyl,
 cyano, halo, haloalkyl, haloalkoxy, haloalkylthio, amino, aminoalkyl,
 15 alkylamino, amidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl,
 alkoxyamino, thiol, and alkylthio;
 R^2 is Z^0-Q ;
 Z^0 is selected from the group consisting of covalent single bond,
 $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 3, $(CH(R^{41}))_g-$
 20 $W^0-(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0
 through 3 and W^0 is selected from the group consisting of O, S, C(O), S(O),
 $N(R^{41})$, and $ON(R^{41})$, and $(CH(R^{41}))_e-W^{22}-(CH(R^{42}))_h$ wherein e and h
 are integers independently selected from 0 through 1 and W^{22} is selected from
 the group consisting of $CR^{41}=CR^{42}$, 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-
 25 cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-
 morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-

morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the proviso that Z^0 is directly bonded to the pyrazinone ring;

R^{41} and R^{42} are independently selected from the group consisting of amidino, hydroxyamino, hydrido, hydroxy, amino, and alkyl;

10 Q is selected from the group consisting of hydrido, with the proviso that Z^0 is other than a covalent single bond, and the formula (II):



wherein D^1 , D^2 , J^1 , J^2 and K^1 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is O, no more than one of D^1 , D^2 , J^1 , J^2 and K^1 is S, one of D^1 , D^2 , J^1 , J^2 and K^1 must be a covalent bond when two of D^1 , D^2 , J^1 , J^2 and K^1 are O and S, and no more than four of D^1 , D^2 , J^1 , J^2 and K^1 are N, with the proviso that R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the divalent nature of sulfur, and the divalent nature of oxygen;

20

K is $(CR^{4a}R^{4b})_n$ wherein n is an integer selected from 1 through 2;

- Q^b is selected from the group consisting of $NR^{20}R^{21}$, aminoalkylenyl, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy, amino, alkylamino, or dialkylamino at the same time and that no more than one of R^{23} and R^{24} is hydroxy, amino, alkylamino, or dialkylamino at the same time;
- R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, aminoalkylenyl, amino, dialkylamino, alkylamino, and hydroxyalkyl;
- Q^s is selected from the group consisting of a single covalent bond, $(CR^{37}R^{38})_b$ wherein b is an integer selected from 1 through 4, and $(CH(R^{14}))_c-W^1-(CH(R^{15}))_d$ wherein c and d are integers independently selected from 1 through 3 and W^1 is selected from the group consisting of $C(O)N(R^{14})$, $(R^{14})NC(O)$, $S(O)$, $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, and $N(R^{14})$, with the provisos that R^{14} is selected from other than halo when directly bonded to N and that $(CR^{37}R^{38})_b$ and $(CH(R^{14}))_c$ are bonded to E^0 ;
- R^{14} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;
- R^{37} and R^{38} are independently selected from the group consisting of hydrido, alkyl, and haloalkyl;
- R^{38} is optionally selected from the group consisting of aroyl and heteroaroyl;

Y^0 is optionally Q^b-Q^{ss} wherein Q^{ss} is $(CH(R^{14}))_e-W^2-(CH(R^{15}))_h$.

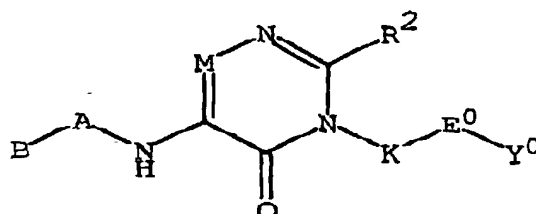
wherein e and h are integers independently selected from 1 through 2 and W^2 is $CR^{4a}=CR^{4b}$ with the proviso that $(CH(R^{14}))_e$ is bonded to E^0 ;

Y^0 is optionally selected from the group consisting of Q^b-Q^{sssr} and Q^b-Q^{sssr} wherein Q^{sssr} is $(CH(R^{38}))_r-W^5$ and Q^{sssr} is $(CH(R^{38}))_r-W^6$, r is an

- 5 integer selected from 1 through 2, and W^5 and W^6 are independently selected from the group consisting of 1,4-indenyl, 1,5-indenyl, 1,6-indenyl, 1,7-indenyl, 2,7-indenyl, 2,6-indenyl, 2,5-indenyl, 2,4-indenyl, 3,4-indenyl, 3,5-indenyl, 3,6-indenyl, 3,7-indenyl, 2,4-benzofuranyl, 2,5-benzofuranyl, 2,6-benzofuranyl, 2,7-benzofuranyl, 3,4-benzofuranyl, 3,5-benzofuranyl, 3,6-benzofuranyl, 3,7-benzofuranyl, 2,4-benzothiophenyl, 2,5-benzothiophenyl, 2,6-benzothiophenyl, 2,7-benzothiophenyl, 3,4-benzothiophenyl, 3,5-benzothiophenyl, 3,6-benzothiophenyl, 3,7-benzothiophenyl, 2,7-imidazo(1,2-a)pyridinyl, 3,4-imidazo(1,2-a)pyridinyl, 3,5-imidazo(1,2-a)pyridinyl, 3,6-imidazo(1,2-a)pyridinyl, 3,7-imidazo(1,2-a)pyridinyl, 2,4-indolyl, 2,5-indolyl, 2,6-indolyl, 2,7-indolyl, 3,4-indolyl, 3,5-indolyl, 3,6-indolyl, 3,7-indolyl, 1,4-isoindolyl, 1,5-isoindolyl, 1,6-isoindolyl, 2,4-isoindolyl, 2,5-isoindolyl, 2,6-isoindolyl, 2,7-isoindolyl, 1,3-isoindolyl, 3,4-indazolyl, 3,5-indazolyl, 3,6-indazolyl, 3,7-indazolyl, 2,4-benzoxazolyl, 2,5-benzoxazolyl, 2,6-benzoxazolyl, 2,7-benzoxazolyl, 3,4-benzisoxazolyl, 3,5-benzisoxazolyl, 3,6-benzisoxazolyl, 3,7-benzisoxazolyl, 1,4-naphthyl, 1,5-naphthyl, 1,6-naphthyl, 1,7-naphthyl, 1,8-naphthyl, 2,4-naphthyl, 2,5-naphthyl, 2,6-naphthyl, 2,7-naphthyl, 2,8-naphthyl, 2,4-quinoliny, 2,5-quinoliny, 2,6-quinoliny, 2,7-quinoliny, 2,8-quinoliny, 3,4-quinoliny, 3,5-quinoliny, 3,6-quinoliny, 3,7-quinoliny, 3,8-quinoliny, 4,5-quinoliny, 4,6-quinoliny, 4,7-quinoliny, 4,8-quinoliny, 1,4-isoquinoliny, 1,5-isoquinoliny, 1,6-isoquinoliny, 1,7-isoquinoliny, 1,8-isoquinoliny, 3,4-isoquinoliny, 3,5-isoquinoliny, 3,6-isoquinoliny, 3,7-isoquinoliny, 3,8-isoquinoliny, 4,5-isoquinoliny, 4,6-isoquinoliny, 4,7-isoquinoliny, 4,8-isoquinoliny, 3,4-cinnoliny, 3,5-cinnoliny, 3,6-cinnoliny, 3,7-cinnoliny, 3,8-cinnoliny, 4,5-cinnoliny, 4,6-cinnoliny, 4,7-cinnoliny, and 4,8-cinnoliny, and each carbon and hyrido containing nitrogen member of the ring

- of the W^5 and of the ring of the W^6 , other than the points of attachment of W^5 and W^6 , is optionally substituted with one or more of the group consisting of R^9 , R^{10} , R^{11} , and R^{12} , with the provisos that Q^b is bonded to lowest number substituent position of each W^5 , Q^b is bonded to highest number substituent position of each W^6 , and $(CH(R^{38}))_r$ is bonded to E^0 .

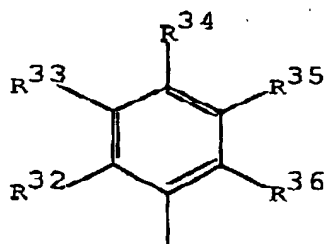
2. The compound as recited in Claim 1 having the Formula:



or a pharmaceutically acceptable salt thereof, wherein;

10

B is the Formula:



R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the

- group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkylenedioxy, haloalkylthio, alkanoyloxy, alkoxy, hydroxy, amino, alkoxyamino, haloalkanoyl, nitro, lower alkylamino, alkylthio, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, alkenyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyalkyl, alkylamino, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

B is optionally selected from the group consisting of hydrido, trialkylsilyl, C2-C8 alkyl, C3-C8 alkylenyl, C3-C8 alkenyl, C3-C8 alkynyl, and C2-C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of

- 5 attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

- B is selected from the group consisting of C3-C12 cycloalkyl and C4-heterocyclyl, wherein each ring carbon may be optionally substituted with R^{33} , a ring carbon other than the ring carbon at the point of attachment of B to A
- 10 may be optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbons and nitrogens adjacent to the carbon at the point of attachment may be optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment may be substituted with R^{10} , a ring carbon
- 15 or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment may be substituted with R^{12} , a ring carbon three atoms from the point of attachment and adjacent to the R^{10} position may be substituted with R^{11} , a ring carbon three atoms from the point of attachment and adjacent to the R^{12} position may be substituted with R^{33} , and a ring carbon four atoms
- 20 from the point of attachment and adjacent to the R^{11} and R^{33} positions may be substituted with R^{34} ;

- R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, alkoxyamino, alkanoyl, haloalkanoyl, amidino, guanidino, alkylenedioxy, haloalkylthio,
- 25 alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfamido, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl,

dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, carboxamido, and cyano;

R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are optionally selected from the group

consisting of heteroaryl and heterocyclyl with the proviso that R^9 , R^{10} , R^{11} ,

5 R^{12} , and R^{13} are substituents for other than B;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of O, S, C(O), $(R^7)NC(O)$, $(R^7)NC(S)$, and $N(R^7)$;

10 R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, hydroxy, halo, alkyl, and haloalkyl;

M is selected from the group consisting of N and R^1-C ;

15 R^1 is selected from the group consisting of hydrido, alkyl, cyano, halo, haloalkyl, haloalkoxy, amino, aminoalkyl, alkylamino, amidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, and alkylthio;

R^2 is Z^0-Q ;

20 Z^0 is selected from the group consisting of covalent single bond and $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 2, $(CH(R^{41}))_g-W^0-(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0 through 3 and W^0 is selected from the group consisting of O, S, and $N(R^{41})$, and $(CH(R^{41}))_e-W^{22}-(CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 1 and W^{22} is selected from the group consisting of

CR⁴¹=CR⁴², 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the proviso that Z⁰ is directly bonded to the pyrazinone ring;

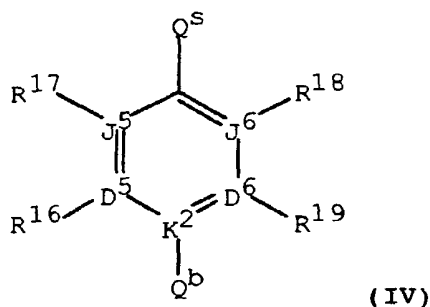
10 R⁴¹ and R⁴² are independently selected from the group consisting of hydrido, hydroxy, and amino;

Q is selected from the group consisting of hydrido, with the proviso that Z⁰ is other than a covalent single bond, aryl, and heteroaryl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R⁹, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R¹³, a carbon adjacent to R⁹ and two atoms from the carbon at the point of attachment is optionally substituted by R¹⁰, a carbon adjacent to R¹³ and two atoms from the carbon at the point of attachment is optionally substituted by R¹², and any carbon adjacent to both R¹⁰ and R¹² is optionally substituted by R¹¹;

K is CHR^{4a} wherein R^{4a} is selected from the group consisting of hydrido, hydroxyalkyl, alkyl, alkoxyalkyl, alkylthioalkyl, and haloalkyl;

E⁰ is selected from the group consisting of a covalent single bond, C(O)N(H), (H)NC(O), (R⁷)NS(O)₂, and S(O)₂N(R⁷);

25 Y⁰ is formula (IV):



- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one can be a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 can be O, no more than one of D^5 , D^6 , J^5 , and J^6 can be S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 can be N, with the provisos that R^{16} , R^{17} , R^{18} , and R^{19} are each independently selected to maintain the tetravalent nature of carbon, trivalent nature of nitrogen, the
10. divalent nature of sulfur, and the divalent nature of oxygen;

- R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;
- 15

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

- Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$, with the
- 20 provisos that no more than one of R^{20} and R^{21} is hydroxy, amino, alkylamino, or

dialkylamino at the same time and that no more than one of R^{23} and R^{24} is hydroxy, amino, alkylamino, or dialkylamino at the same time;

R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, amino, alkylamino and dialkylamino;

5 Q^s is selected from the group consisting of a single covalent bond,

$(CR^{37}R^{38})_b$ wherein b is an integer selected from 1 through 4, and

$(CH(R^{14}))_c-W^1-(CH(R^{15}))_d$ wherein c and d are integers independently

selected from 1 through 3 and W^1 is selected from the group consisting of

$C(O)N(R^{14})$, $(R^{14})NC(O)$, $S(O)$, $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, and

10 $N(R^{14})$, with the provisos that R^{14} is selected from other than halo when

directly bonded to N and that $(CR^{37}R^{38})_b$, and $(CH(R^{14}))_c$ are bonded to E^0 ;

R^{14} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

R^{37} and R^{38} are independently selected from the group consisting of

15 hydrido, alkyl, and haloalkyl;

R^{38} is optionally selected from the group consisting of aroyl and heteroaroyl;

Y^0 is optionally Q^b-Q^{ss} wherein Q^{ss} is $(CH(R^{14}))_e-W^2-(CH(R^{15}))_h$,

wherein e and h are integers independently selected from 1 through 2 and W^2

20 is $CR^{4a}=CH$ with the proviso that $(CH(R^{14}))_e$ is bonded to E^0 .

3. The compound as recited in Claim 2 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, trialkylsilyl, C2-C8 alkyl, C3-C8 alkylenyl, C3-C8 alkenyl, C3-C8 alkynyl, and C2-C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to

and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

A is $(CH(R^{15}))_{pa}-W^7$ wherein pa is an integer selected from 1 through 3 and W^7 is selected from the group consisting of O, S, and $N(R^7)$ wherein R^7 is selected from the group consisting of hydrido and alkyl;

R^{15} is selected from the group consisting of hydrido, hydroxy, halo, alkyl, and haloalkyl with the proviso that R^{15} is other than hydroxy and halo when R^{15} is on the carbon bonded directly to W^7 ;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, alkyl, cyano, halo, haloalkyl, haloalkoxy, amino, aminoalkyl, alkylamino, amidino, hydroxy, hydroxyamino, alkoxy, hydroxyalkyl, alkoxyamino, thiol, and alkylthio;

R^2 is Z^0-Q ;

Z^0 is selected from the group consisting of covalent single bond and $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 2;

R^{41} and R^{42} are independently selected from the group consisting of hydrido, hydroxy, and amino;

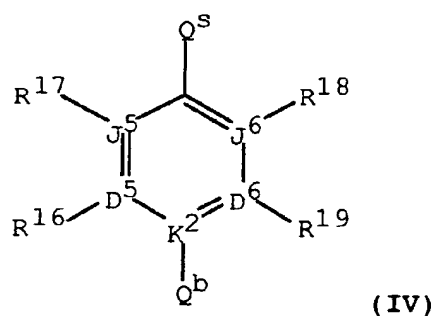
Q is selected from the group consisting of aryl and heteroaryl, wherein a carbon adjacent to the carbon at the point of attachment is optionally

- substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

- R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, alkoxyamino, alkanoyl, haloalkanoyl, amidino, guanidino, alkylenedioxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfamido, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, carboxamido, and cyano;

- K is CHR^{4a} wherein R^{4a} is selected from the group consisting of hydrido, hydroxyalkyl, alkyl, alkoxyalkyl, alkylthioalkyl, and haloalkyl; E^0 is selected from the group consisting of a covalent single bond, $C(O)N(H)$, $(H)NC(O)$, $(R^7)NS(O)_2$, and $S(O)_2N(R^7)$;

Y^0 is formula (IV):



- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more

than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N;

5 R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkylamino, and cyano;

10 R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy, amino, alkylamino, or dialkylamino at the same time and that no more than one of R^{23} and R^{24} is hydroxy, amino, alkylamino, or dialkylamino at the same time;

R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, alkyl, hydroxy, amino, alkylamino and dialkylamino;

Q^s is selected from the group consisting of a single covalent bond,

20 $(CR^{37}R^{38})_b$ wherein b is an integer selected from 1 through 3, and

$(CH(R^{14}))_c-W^1-(CH(R^{15}))_d$ wherein c and d are integers independently

selected from 1 through 2 and W^1 is selected from the group consisting of

$C(O)N(R^{14})$, $(R^{14})NC(O)$, $S(O)$, $S(O)_2$, $S(O)_2N(R^{14})$, $N(R^{14})S(O)_2$, and

$N(R^{14})$, with the provisos that R^{14} is selected from other than halo when directly bonded to N and that $(CR^{37}R^{38})_b$, and $(CH(R^{14}))_c$ are bonded to E^0 ;

R^{14} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

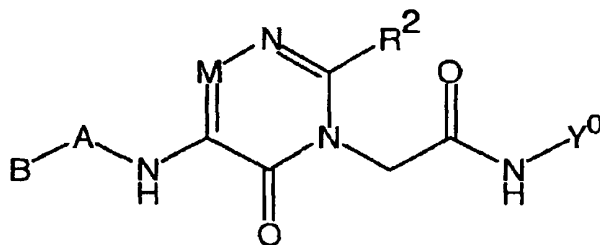
5 R^{37} and R^{38} are independently selected from the group consisting of hydrido, alkyl, and haloalkyl;

R^{38} is optionally selected from the group consisting of aroyl and heteroaroyl;

Y^0 is optionally Q^b-Q^{ss} wherein Q^{ss} is $(CH(R^{14}))_e-W^2-(CH(R^{15}))_h$,

10 wherein e and h are integers independently selected from 1 through 2 and W^2 is $CR^{4a}=CH$ with the proviso that $(CH(R^{14}))_e$ is bonded to E^0 .

4. The compound as recited in Claim 3 having the Formula:



15 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, trialkylsilyl, C2-C4 alkyl, C3-C5 alkylenyl, C3-C4 alkenyl, C3-C4 alkynyl, and C2-C4 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 3 atoms from the point of attachment of B to A with one or more

20 of the group consisting of R^{32} , R^{33} , and R^{34} ;

R^{32} , R^{33} , and R^{34} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl,

monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, and cyano;

A is $(\text{CH}(\text{R}^{15}))_{\text{pa}}-\text{N}(\text{R}^7)$ wherein pa is an integer selected from 1 through 2 and R^7 is selected from the group consisting of hydrido and alkyl;

5 R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, 10 alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

R^2 is Z^0-Q ;

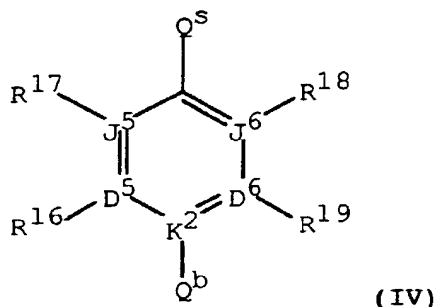
Z^0 is selected from the group consisting of covalent single bond and CH_2 ;

15 Q is selected from the group consisting of aryl and heteroaryl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

20 R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

- R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl,
- 5 hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

Y^0 is formula (IV):



- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N;
- 15 R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;
- 20 R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

5 R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, alkyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH_2 , and CH_2CH_2 .

10 5. The compound as recited in Claim 4 having the Formula or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, trimethylene, tetramethylene, butyl, 2-butenyl, 3-butenyl, 2-butyne, sec-butyl, *tert*-butyl, isobutyl, 2-methylpropenyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, and 2,2-difluoropropyl, wherein each
15 member of group B is optionally substituted at any carbon up to and including 3 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , and R^{34} ;

R^{32} , R^{33} , and R^{34} are independently selected from the group
20 consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro,
25 bromo, amidosulfonyl, N-methylamidulosulfonyl, N,N-dimethylamidulosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

A is selected from the group consisting of single covalent bond, NH, and N(CH₃);

M is selected from the group consisting of N and R¹-C;

R¹ is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, 1-aminoethyl, methylamino, dimethylamino, cyano, methyl, ethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, methoxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxyamino, methylthio, ethylthio, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, and bromo;

10 R² is Z⁰-Q;

Z⁰ is selected from the group consisting of a covalent single bond and CH₂;

Q is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R⁹, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R¹³, a carbon adjacent to R⁹ and two atoms from the carbon at the point of attachment is optionally substituted by R¹⁰, a carbon adjacent to R¹³ and two atoms from the carbon at the point of attachment is optionally substituted by R¹², and any carbon adjacent to both R¹⁰ and R¹² is optionally substituted by R¹¹;

25 R⁹, R¹¹, and R¹³ are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio,

trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidossulfonyl, N,N-dimethylamidossulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

- 5 R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methanesulfonamido, amidosulfonyl, N-methylamidossulfonyl, N,N-dimethylamidossulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, 15 amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group consisting of:

- 1-Q^b-4-Q^s-2-R¹⁶-3-R¹⁷-5-R¹⁸-6-R¹⁹ benzene,
 2-Q^b-5-Q^s-6-R¹⁷-4-R¹⁸-2-R¹⁹ pyridine,
 20 3-Q^b-6-Q^s-2-R¹⁶-5-R¹⁸-4-R¹⁹ pyridine, 2-Q^b-4-Q^s-3-R¹⁶-6-R¹⁸ pyrazine,
 3-Q^b-6-Q^s-2-R¹⁸-5-R¹⁸-4-R¹⁹ pyridazine,
 2-Q^b-5-Q^s-6-R¹⁷-4-R¹⁸ pyrimidine, 5-Q^b-2-Q^s-3-R¹⁶-6-R¹⁹ pyrimidine,
 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ thiophene, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ thiophene,
 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ furan, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ furan,
 25 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ pyrrole, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ pyrrole,
 4-Q^b-2-Q^s-5-R¹⁹ imidazole, 2-Q^b-4-Q^s-5-R¹⁷ imidazole,
 3-Q^b-5-Q^s-4-R¹⁶ isoxazole, 5-Q^b-3-Q^s-4-R¹⁶ isoxazole,

2-Q^b-5-Q^s-4R¹⁶ pyrazole, 4-Q^b-2-Q^s-5-R¹⁹ thiazole, and
2-Q^b-5-Q^s-4R¹⁷ thiazole;

R¹⁶, R¹⁷, R¹⁸, and R¹⁹ are independently selected from the group
consisting of hydrido, methyl, ethyl, isopropyl, propyl, carboxy, amidino,
5 guanidino, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino,
aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino,
N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio,
methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl,
10 pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl,
trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo,
amidosulfonyl, N-methylamidulosulfonyl, N,N-dimethylamidulosulfonyl,
hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-
hydroxyethyl, and cyano;

R¹⁶ and R¹⁹ are optionally Q^b with the proviso that no more than one
15 of R¹⁶ and R¹⁹ is Q^b at the same time and that Q^b is Q^{be};

Q^b is selected from the group consisting of NR²⁰R²¹, Q^{be} wherein
Q^{be} is hydrido, C(NR²⁵)NR²³R²⁴, and N(R²⁶)C(NR²⁵)N(R²³)(R²⁴), with
the provisos that no more than one of R²⁰, R²¹, R²³, and R²⁴ can be
hydroxy, when any two of the group consisting of R²⁰, R²¹, R²³, and R²⁴
20 are bonded to the same atom and that said Q^b group is bonded directly to a
carbon atom;

R²⁰, R²¹, R²³, R²⁴, R²⁵, and R²⁶ are independently selected from the
group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond,
25 CH₂, and CH₂CH₂.

R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

R^9 , R^{11} , and R^{13} are independently selected from the group consisting

- 5 of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-
- 10 pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidulosulfonyl, N,N-dimethylamidulosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of

- 15 hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methanesulfonamido, amidosulfonyl, N-methylamidulosulfonyl, N,N-
- 20 dimethylamidulosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group consisting of:

- 25 $1-Q^b-4-Q^s-2-R^{16}-3-R^{17}-5-R^{18}-6-R^{19}$ benzene,
- $2-Q^b-5-Q^s-6-R^{17}-4-R^{18}-2-R^{19}$ pyridine,
- $3-Q^b-6-Q^s-2-R^{16}-5-R^{18}-4-R^{19}$ pyridine, $2-Q^b-4-Q^s-3-R^{16}-6-R^{18}$ pyrazine,
- $3-Q^b-6-Q^s-2-R^{18}-5-R^{18}-4-R^{19}$ pyridazine,

- $2-Q^b-5-Q^s-6-R^{17}-4-R^{18}$ pyrimidine, $5-Q^b-2-Q^s-3-R^{16}-6-R^{19}$ pyrimidine,
 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ thiophene, $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ thiophene,
 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ furan, $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ furan,
 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ pyrrole, $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ pyrrole,
5 $4-Q^b-2-Q^s-5-R^{19}$ imidazole, $2-Q^b-4-Q^s-5-R^{17}$ imidazole,
 $3-Q^b-5-Q^s-4-R^{16}$ isoxazole, $5-Q^b-3-Q^s-4-R^{16}$ isoxazole,
 $2-Q^b-5-Q^s-4-R^{16}$ pyrazole, $4-Q^b-2-Q^s-5-R^{19}$ thiazole, and
 $2-Q^b-5-Q^s-4-R^{17}$ thiazole;
- R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group
- 10 consisting of hydrido, methyl, ethyl, isopropyl, propyl, amidino, guanidino,
 methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, aminomethyl, 1-
 aminoethyl, 2-aminoethyl, N-N-methylamino, dimethylamino, N-ethylamino,
 methylthio, ethylthio, isopropylthio, trifluoromethylthio, methylsulfinyl,
 ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl, pentafluoroethyl,
 15 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-
 tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-
 methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-
 hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano;
- Q^b is selected from the group consisting of $NR^{20}R^{21}$,
- 20 $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos
 that no more than one of R^{20} , R^{21} , R^{23} , and R^{24} can be hydroxy, when any
 two of the group consisting of R^{20} , R^{21} , R^{23} , and R^{24} are bonded to the
 same atom and that said Q^b group is bonded directly to a carbon atom;

R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

Q^5 is selected from the group consisting of a single covalent bond,

5 CH_2 , and CH_2CH_2 .

7. The compound as recited in Claim 6 or a pharmaceutically acceptable salt thereof, wherein;

A is selected from the group consisting of $CH_2N(CH_3)$,

10 $CH_2N(CH_2CH_3)$, $CH_2CH_2N(CH_3)$, and $CH_2CH_2N(CH_2CH_3)$;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, methylamino, cyano, methyl, trifluoromethyl, methoxy, hydroxymethyl, methoxyamino, methylthio,

15 trifluoromethoxy, fluoro, and chloro;

R^2 is Z^0-Q ;

Z^0 is selected from the group consisting of covalent single bond and

CH_2 ;

Q is selected from the group consisting of 5-amino-3-

20 amidocarbonylphenyl, 5-amino-2-fluorophenyl, 3-amino-5-hydroxymethylphenyl, 5-amino-3-methoxycarbonylphenyl, 3-amidinophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, benzyl, 3-carboxyphenyl, 3-carboxy-5-hydroxyphenyl, 3-carboxy-5-aminophenyl, 3-chlorophenyl, 2-chlorophenyl, 3-cyanophenyl, 3-

25 dimethylaminophenyl, 2-fluorophenyl, 3-fluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl,

2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;

Y^0 is selected from the group consisting of:

1- Q^b -4- Q^s -2- R^{16} -3- R^{17} -5- R^{18} -6- R^{19} benzene,

5 2- Q^b -5- Q^s -6- R^{17} -4- R^{18} -2- R^{19} pyridine,

3- Q^b -6- Q^s -2- R^{16} -5- R^{18} -4- R^{19} pyridine,

3- Q^b -5- Q^s -4- R^{16} -2- R^{19} thiophene, and 2- Q^b -5- Q^s -3- R^{16} -4- R^{17} thiophene;

R^{16} and R^{19} are independently selected from the group consisting of

hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy,

10 hydroxymethyl, fluoro, chloro, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one

of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

R^{17} and R^{18} are independently selected from the group consisting of

hydrido, fluoro, chloro; hydroxy, hydroxymethyl, amino, carboxy, and cyano;

15 Q^b is selected from the group consisting of Q^{be} wherein Q^{be} is hydrido

and $C(NR^{25})NR^{23}R^{24}$;

R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of

hydrido and methyl;

Q^s is CH_2 .

20

8. A compound as recited in Claim 7 or a pharmaceutically acceptable salt thereof where said compound is selected from the group consisting of:

2-[3-[2-[3-aminophenyl]-6-chloro-N-[[4-iminomethylphenyl]methyl]-

25 5-[N,N-dimethylhydrazino]-4-oxo-1(4H)-pyrimidinyl]]acetamide;

2-[3-[2-[3-aminophenyl]-6-chloro-5-[N-ethyl-N-methylhydrazino]-N-[[4-iminomethylphenyl]methyl]-4-oxo-1(4H)-pyrimidinyl]]acetamide;

WO 00/69832

PCT/US00/09806

haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is

- 5 an integer selected from 0 through 3, and W^7 is selected from the group consisting of $(R^7)NC(O)$ and $N(R^7)$;

R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

- 10 M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

- 15 R^2 is Z^0-Q ;

Z^0 is selected from the group consisting of a covalent single bond, O, S, NH, and CH_2 ;

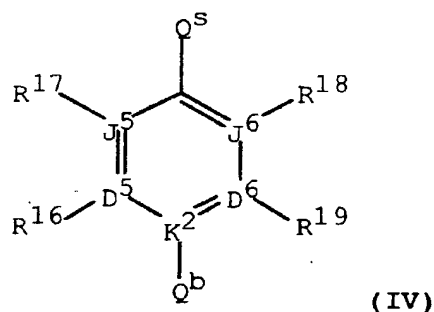
Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted

- 20 by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is
- 25 optionally substituted by R^{11} ;

- R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

- R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

Y^0 is formula (IV):



- wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N;
- R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl,

alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

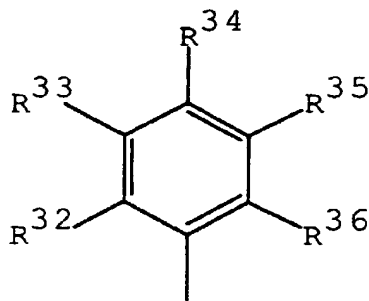
5 Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

10 R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, alkyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH_2 , and CH_2CH_2 .

10. The compound as recited in Claim 9 or a pharmaceutically acceptable salt thereof, wherein;

B is the Formula:



20 R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-

trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl,
 5 methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b;

A is selected from the group consisting of single covalent bond, NH, N(CH₃), N(OH), CH₂, CH₃CH, CF₃CH, NHC(O), N(CH₃)C(O), C(O)NH, C(O)N(CH₃), CH₂CH₂, CH₂CH₂CH₂, CH₃CHCH₂, and
 10 CF₃CHCH₂;

M is selected from the group consisting of N and R¹-C;

R¹ is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, 1-aminoethyl, methylamino, dimethylamino, cyano, methyl, ethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, methoxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl,
 15 methoxyamino, methylthio, ethylthio, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, and bromo;

R² is Z⁰-Q;

Z⁰ is selected from the group consisting of a covalent single bond, O,
 20 S, NH, and CH₂;

Q is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl,
 25 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R⁹, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R¹³, a carbon adjacent to R⁹ and two atoms from the carbon at

the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

5 R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-

10 pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidulosulfonyl, N,N-dimethylamidulosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

15 R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino,

20 methanesulfonamido, amidosulfonyl, N-methylamidulosulfonyl, N,N-dimethylamidulosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

25 Y^0 is selected from the group consisting of:

$1-Q^b-4-Q^s-2-R^{16}-3-R^{17}-5-R^{18}-6-R^{19}$ benzene,

$2-Q^b-5-Q^s-6-R^{17}-4-R^{18}-2-R^{19}$ pyridine,

- $3-Q^b-6-Q^s-2-R^{16}-5-R^{18}-4-R^{19}$ pyridine, $2-Q^b-4-Q^s-3-R^{16}-6-R^{18}$ pyrazine, $3-Q^b-6-Q^s-2-R^{18}-5-R^{18}-4-R^{19}$ pyridazine,
 $2-Q^b-5-Q^s-6-R^{17}-4-R^{18}$ pyrimidine, $5-Q^b-2-Q^s-3-R^{16}-6-R^{19}$ pyrimidine,
 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ thiophene, $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ thiophene,
 5 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ furan, $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ furan,
 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ pyrrole, $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ pyrrole,
 $4-Q^b-2-Q^s-5-R^{19}$ imidazole, $2-Q^b-4-Q^s-5-R^{17}$ imidazole,
 $3-Q^b-5-Q^s-4-R^{16}$ isoxazole, $5-Q^b-3-Q^s-4-R^{16}$ isoxazole,
 $2-Q^b-5-Q^s-4-R^{16}$ pyrazole, $4-Q^b-2-Q^s-5-R^{19}$ thiazole, and
 10 $2-Q^b-5-Q^s-4-R^{17}$ thiazole;

- R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, isopropyl, propyl, carboxy, amidino, guanidino, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino,
 15 N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl,
 20 hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

- Q^b is selected from the group consisting of Q^{be} wherein Q^{be} is hydrido
 25 and $C(NR^{25})NR^{23}R^{24}$, with the proviso that no more than one of R^{23} and R^{24} is hydroxy at the same time;

R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, methyl, ethyl, and hydroxy;

Q^5 is selected from the group consisting of a single covalent bond, CH_2 and CH_2CH_2 .

5

11. The compound as recited in Claim 10 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of 2-aminophenyl, 3-aminophenyl, 3-amidinophenyl, 4-amidinophenyl, 3-carboxyphenyl, 3-carboxy-5-hydroxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-methoxyaminophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, and 3-trifluoromethylphenyl;

A is selected from the group consisting of CH_2 , CH_3CH , CF_3CH , $NHC(O)$, CH_2CH_2 , and $CH_2CH_2CH_2$;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, methylamino, cyano, methyl, trifluoromethyl, methoxy, hydroxymethyl, methoxyamino, methylthio, trifluoromethoxy, fluoro, and chloro;

R^2 is Z^0-Q ;

Z^0 is selected from the group consisting of a covalent single bond, O, S, NH, and CH_2 ;

Q is selected from the group consisting of 5-amino-3-amidocarbonylphenyl, 5-amino-2-fluorophenyl, 3-amino-5-hydroxymethylphenyl, 5-amino-3-methoxycarbonylphenyl, 3-amidinophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, benzyl, 3-carboxyphenyl, 3-carboxy-5-aminophenyl, 3-carboxy-5-hydroxyphenyl, 3-carboxymethyl-5-aminophenyl, 3-carboxymethyl-5-

hydroxyphenyl, 3-carboxymethylphenyl, 3-chlorophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 3-cyanophenyl, 3-dimethylaminophenyl, 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;

10 Y^0 is selected from the group consisting of:

1- Q^b -4- Q^s -2- R^{16} -3- R^{17} -5- R^{18} -6- R^{19} benzene,
 2- Q^b -5- Q^s -6- R^{17} -4- R^{18} -2- R^{19} pyridine,
 3- Q^b -6- Q^s -2- R^{16} -5- R^{18} -4- R^{19} pyridine,
 3- Q^b -5- Q^s -4- R^{16} -2- R^{19} thiophene, and 2- Q^b -5- Q^s -3- R^{16} -4- R^{17} thiophene;

15 R^{16} and R^{19} are independently selected from the group consisting of hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, hydroxymethyl, fluoro, chloro, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

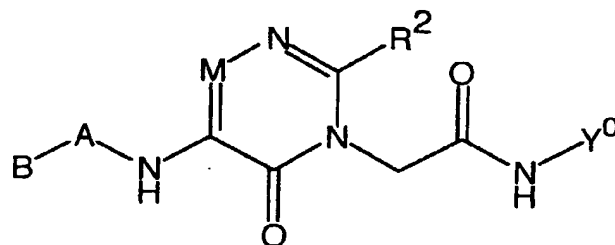
20 R^{17} and R^{18} are independently selected from the group consisting of hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;

Q^b is selected from the group consisting of Q^{be} wherein Q^{be} is hydrido and $C(NR^{25})NR^{23}R^{24}$;

R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of
 25 hydrido and methyl;

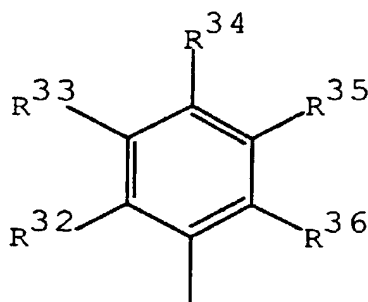
Q^s is CH_2 .

12. The compound as recited in Claim 9 having the Formula:



or a pharmaceutically acceptable salt thereof, wherein;

B is the Formula:



5

R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the

group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

10

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is $N(R^7)$;

15

R^7 is selected from the group consisting of hydrido and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

5 R^2 is Z^0 -Q;

Z^0 is a covalent single bond;

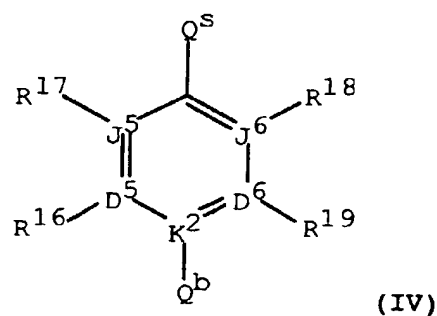
Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is

10 optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

15 R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkylamid sulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

20 R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, 25 carboxy, carboxyamido, carboxyalkyl, and cyano;

Y^0 is formula (IV):



wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N;

R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

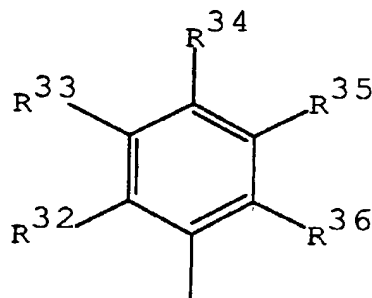
Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido and alkyl;

Q^s is CH_2 .

13. The compound as recited in Claim 12 or a pharmaceutically acceptable salt thereof, wherein;

B is the Formula:



5 R³², R³³, R³⁴, R³⁵, and R³⁶ are independently selected from the group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, 10 amidocarbonyl, carboxy, cyano, and Q^b;

A is selected from the group consisting of single covalent bond, NH, N(CH₃), CH₂, CH₃CH, and CH₂CH₂;

M is selected from the group consisting of N and R¹-C;

15 R¹ is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, methylamino, cyano, methyl, trifluoromethyl, methoxy, hydroxymethyl, methoxyamino, methylthio, trifluoromethoxy, fluoro, and chloro;

20 R² is selected from the group consisting of phenyl, 2-thienyl, 2-furyl, 2-pyrrolyl, 2-imidazolyl, 2-thiazolyl, 3-isoxazolyl, 2-pyridyl, and 3-pyridyl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R⁹, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R¹³, a carbon adjacent to R⁹ and two atoms from the carbon at the point of attachment is optionally substituted by

R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

- R^9 , R^{11} , and R^{13} are independently selected from the group consisting
- 5 of hydrido, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, methylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, hydroxymethyl, 1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, carboxy, and cyano;
- 10 R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, amidocarbonyl, N-methylamidocarbonyl, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, carboxy, carboxymethyl, amino, acetamido, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoroacetamido, aminomethyl, N-
- 15 methylamino, dimethylamino, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, methoxycarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group consisting of:

- 1-Q^b-4-Q^s-2-R¹⁶-3-R¹⁷-5-R¹⁸-6-R¹⁹ benzene,
- 2-Q^b-5-Q^s-6-R¹⁷-4-R¹⁸-2-R¹⁹ pyridine, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ thiophene,
- 20 3-Q^b-6-Q^s-2-R¹⁶-5-R¹⁸-4-R¹⁹ pyridine, 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ thiophene,
- 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ furan, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ furan,
- 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ pyrrole, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ pyrrole,
- 4-Q^b-2-Q^s-5-R¹⁹ thiazole, and 2-Q^b-5-Q^s-4-R¹⁷ thiazole;

- R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group
- 25 consisting of hydrido, methyl, ethyl, amidino, guanidino, methoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethylthio, methylsulfinyl,

methanesulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoromethoxy, fluoro, chloro, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, carboxy, and cyano.

Q^b is selected from the group consisting of $NR^{20}R^{21}$ and

- 5 $C(NR^{25})NR^{23}R^{24}$, with the proviso that said Q^b group is bonded directly to a carbon atom;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, methyl, and ethyl;

Q^s is CH_2 .

10

14. The compound as recited in Claim 13 or a pharmaceutically acceptable salt thereof, wherein;

- 15 B is selected from the group consisting of 2-aminophenyl, 3-aminophenyl, 3-amidinophenyl, 4-amidinophenyl, 3-carboxyphenyl, 3-carboxy-5-hydroxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-methoxyaminophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-methylphenyl, 4-methylphenyl, and phenyl;

A is selected from the group consisting of CH_2 , CH_3CH , CF_3CH ,

- 20 $NHC(O)$, CH_2CH_2 , and $CH_2CH_2CH_2$;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, amino, methyl, trifluoromethyl, fluoro, and chloro;

- 25 R^2 is selected from the group consisting of 5-amino-3-amidocarbonylphenyl, 5-amino-2-fluorophenyl, 3-amino-5-hydroxymethylphenyl, 5-amino-3-methoxycarbonylphenyl, 3-amidinophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, benzyl, 3-carboxyphenyl, 3-carboxy-5-aminophenyl, 3-carboxy-5-hydroxyphenyl, 3-carboxymethyl-5-aminophenyl, 3-carboxymethyl-5-hydroxyphenyl, 3-carboxymethylphenyl, 3-chlorophenyl, 2-chlorophenyl, 3-
- 30

cyanophenyl, 3-dimethylaminophenyl, 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylamino-phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;

Y^0 is selected from the group consisting of:

- 10 $1-Q^b-4-Q^s-2-R^{16}-3-R^{17}-5-R^{18}-6-R^{19}$ benzene,
 $2-Q^b-5-Q^s-6-R^{17}-4-R^{18}-2-R^{19}$ pyridine,
 $3-Q^b-6-Q^s-2-R^{16}-5-R^{18}-4-R^{19}$ pyridine,
 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ thiophene, and $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ thiophene;

- R^{16} and R^{19} are independently selected from the group consisting of
 15 hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, hydroxymethyl, fluoro, chloro, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

- R^{17} and R^{18} are independently selected from the group consisting of
 20 hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;

Q^b is selected from the group consisting of Q^{be} wherein Q^{be} is hydrido and $C(NR^{25})NR^{23}R^{24}$;

R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido and methyl;

- 25 Q^s is CH_2 .

15. The compound as recited in Claim 14 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of 3-aminophenyl, 3-amidinophenyl, 4-amidinophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 2-fluorophenyl, 4-methylphenyl, and phenyl;

A is selected from the group consisting of CH_2 , NHC(O) , CH_2CH_2 , and $\text{CH}_2\text{CH}_2\text{CH}_2$;

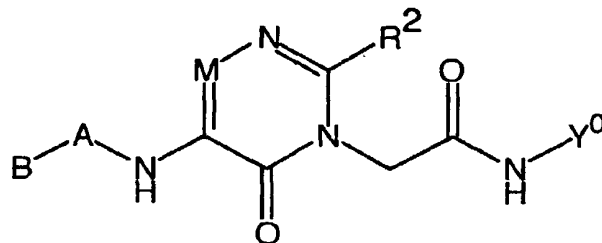
M is selected from the group consisting of N and $\text{R}^1\text{-C}$;

R^1 is selected from the group consisting of hydrido, fluoro, and chloro;

R^2 is selected from the group consisting of 3-aminophenyl, benzyl, 3-chlorophenyl, 3-dimethylaminophenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-bromo-2-thienyl, 2-thienyl, and 3-thienyl;

Y^0 is selected from the group consisting of 5-amidino-2-thienylmethyl, 4-amidinobenzyl, 2-fluoro-4-amidinobenzyl, and 3-fluoro-4-amidinobenzyl.

16. A compound as recited in Claim 9 where said compound is selected from the group having the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^2 is 3-aminophenyl, B is 3-chlorophenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is phenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is phenyl, B is 3-chlorophenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-dimethylaminophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

5 R^2 is 2-methylphenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is phenyl, B is 3-aminophenyl, A is $C(O)NH$, Y^0 is 4-amidinobenzyl, and M is CH;

10 R^2 is phenyl, B is 3-amidinophenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-(N-methylamino)phenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-methylsulfonamidophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

15 R^2 is phenyl, B is 4-amidinophenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-methylaminophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is phenyl, B is phenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

20 R^2 is 3-methylphenyl, B is 4-phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 3-chlorophenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

25 R^2 is 3-aminophenyl, B is phenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

R^2 is phenyl, B is 3-chlorophenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

R^2 is 3-dimethylaminophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

R^2 is 2-methylphenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

5 R^2 is phenyl, B is 3-aminophenyl, A is $C(O)NH$, Y^0 is 4-amidinobenzyl, and M is CCl;

R^2 is phenyl, B is 3-amidinophenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

10 R^2 is 3-(N-methylamino)phenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

R^2 is 3-methylsulfonamidophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

R^2 is phenyl, B is 4-amidinophenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

15 R^2 is 3-methylaminophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

R^2 is phenyl, B is phenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

20 R^2 is 3-methylphenyl, B is 4-phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CCl;

R^2 is 3-aminophenyl, B is 3-chlorophenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 3-aminophenyl, B is phenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

25 R^2 is phenyl, B is 3-chlorophenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 3-dimethylaminophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 2-methylphenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

5 R^2 is phenyl, B is 3-aminophenyl, A is $C(O)NH$, Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is phenyl, B is 3-amidinophenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 3-(N-methylamino)phenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

10 R^2 is 3-methylsulfonamidophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is phenyl, B is 4-amidinophenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

15 R^2 is 3-methylaminophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is phenyl, B is phenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 3-methylphenyl, B is 4-phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

20 R^2 is 3-aminophenyl, B is 3-chlorophenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is phenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is phenyl, B is 3-chlorophenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

25 R^2 is 3-dimethylaminophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 2-methylphenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is phenyl, B is 3-aminophenyl, A is $\text{C}(\text{O})\text{NH}$, Y^0 is 4-amidinobenzyl, and M is N;

5 R^2 is phenyl, B is 3-amidinophenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-(N-methylamino)phenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

10 R^2 is 3-methylsulfonamidophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is phenyl, B is 4-amidinophenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-methylaminophenyl, B is phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

15 R^2 is phenyl, B is phenyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

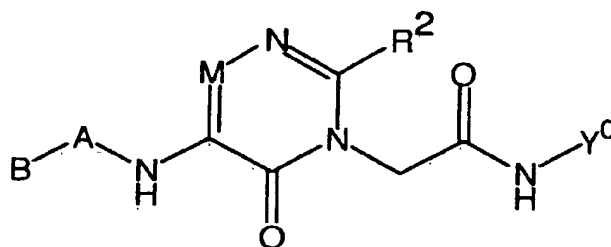
R^2 is 3-methylphenyl, B is 4-phenyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is N.

20

25

30

17. The compound as recited in Claim 2 having the Formula:



or a pharmaceutically acceptable salt thereof, wherein;

5 B is selected from the group consisting of hydrido, C2-C8 alkyl, C3-C8 alkenyl, C3-C8 alkynyl, and C2-C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

10 R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of $(R^7)NC(O)$ and $N(R^7)$;

20 R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

5 R^2 is Z^0 -Q;

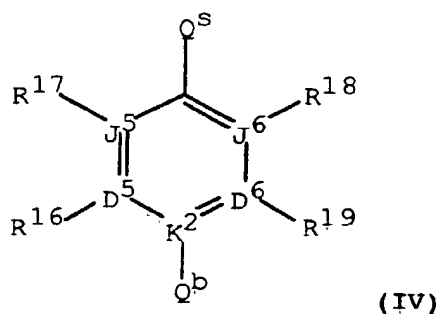
Z^0 is selected from the group consisting of a covalent single bond, O, S, NH, and CH_2 ;

Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted
10 by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is
15 optionally substituted by R^{11} ;

R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, alkoxy, halo, haloalkyl,
20 haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl,
25 hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, amidocarbonyl, halo, haloalkyl, and cyano;

Y^0 is formula (IV):



wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N;

R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $C(NR^{25})NR^{23}R^{24}$, and $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, alkyl, and hydroxy;

Q^5 is selected from the group consisting of a single covalent bond,

CH_2 , and CH_2CH_2 .

18. The compound as recited in Claim 17 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, ethyl, 2-propynyl, 2-propenyl, propyl, isopropyl, butyl, 2-butenyl, 3-butenyl, 2-butylnyl, sec-butyl, *tert*-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentyl, 1-methyl-2-butenyl, 1-methyl-3-butenyl, 1-methyl-2-butylnyl, 3-pentyl, 1-ethyl-2-propenyl, 2-methylbutyl, 2-methyl-2-butenyl, 2-methyl-3-butenyl, 2-methyl-3-butylnyl, 3-methylbutyl, 3-methyl-2-butenyl, 3-methyl-3-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-4-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 1-propyl-2-propenyl, 1-ethyl-2-butylnyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl-4-hexenyl, 1-methyl-5-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-4-pentenyl, 1-butyl-2-propenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-

methanidosulfonyl, N,N-dimethanidosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methanamidocarbonyl, N,N-dimethanamidocarbonyl, cyano, and Q^b ;

- 5 A is selected from the group consisting of single covalent bond, NH, N(CH₃), N(OH), CH₂, CH₃CH, CF₃CH, NHC(O), N(CH₃)C(O), C(O)NH, C(O)N(CH₃), CH₂CH₂, CH₂CH₂CH₂, CH₃CHCH₂, and CF₃CHCH₂;

M is selected from the group consisting of N and R¹-C;

- 10 R¹ is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, 1-aminoethyl, methanamino, dimethanamino, cyano, methyl, ethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, methoxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxyamino, methylthio, ethylthio, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, and bromo;
- 15

R² is Z⁰-Q;

Z⁰ is selected from the group consisting of a covalent single bond, O, S, NH, and CH₂;

- 20 Q is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R⁹, the
- 25 other carbon adjacent to the carbon at the point of attachment is optionally substituted by R¹³, a carbon adjacent to R⁹ and two atoms from the carbon at the point of attachment is optionally substituted by R¹⁰, a carbon adjacent to R¹³ and two atoms from the carbon at the point of attachment is optionally

substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methanesulfonamido, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

Y^0 is selected from the group consisting of:

- 1-Q^b-4-Q^s-2-R¹⁶-3-R¹⁷-5-R¹⁸-6-R¹⁹ benzene,
 25 2-Q^b-5-Q^s-6-R¹⁷-4-R¹⁸-2-R¹⁹ pyridine,
 3-Q^b-6-Q^s-2-R¹⁶-5-R¹⁸-4-R¹⁹ pyridine, 2-Q^b-4-Q^s-3-R¹⁶-6-R¹⁸ pyrazine, 3-Q^b-6-Q^s-2-R¹⁸-5-R¹⁸-4-R¹⁹ pyridazine,
 2-Q^b-5-Q^s-6-R¹⁷-4-R¹⁸ pyrimidine, 5-Q^b-2-Q^s-3-R¹⁶-6-R¹⁹ pyrimidine,

- 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ thiophene, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ thiophene,
 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ furan, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ furan,
 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ pyrrole, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ pyrrole,
 4-Q^b-2-Q^s-5-R¹⁹ imidazole, 2-Q^b-4-Q^s-5-R¹⁷ imidazole,
 5 3-Q^b-5-Q^s-4-R¹⁶ isoxazole, 5-Q^b-3-Q^s-4-R¹⁶ isoxazole,
 2-Q^b-5-Q^s-4-R¹⁶ pyrazole, 4-Q^b-2-Q^s-5-R¹⁹ thiazole, and
 2-Q^b-5-Q^s-4-R¹⁷ thiazole;

- R¹⁶, R¹⁷, R¹⁸, and R¹⁹ are independently selected from the group
 consisting of hydrido, methyl, ethyl, isopropyl, propyl, carboxy, amidino,
 10 guanidino, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino,
 aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino,
 N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio,
 methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl,
 pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl,
 15 trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo,
 amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl,
 hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-
 hydroxyethyl, and cyano;

- R¹⁶ and R¹⁹ are optionally Q^b with the proviso that no more than one of
 20 R¹⁶ and R¹⁹ is Q^b at the same time and that Q^b is Q^{be};

Q^b is selected from the group consisting of NR²⁰R²¹, Q^{be}, wherein Q^{be}
 is hydrido, C(NR²⁵)NR²³R²⁴, and N(R²⁶)C(NR²⁵)N(R²³)(R²⁴), with the
 provisos that no more than one of R²⁰ and R²¹ is hydroxy at the same time and
 that no more than one of R²³ and R²⁴ is hydroxy at the same time;

R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, and hydroxy;

Q^5 is selected from the group consisting of a single covalent bond, CH_2 , and CH_2CH_2 .

5

19. The compound as recited in Claim 18 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butyl, (R)-2-butyl, (S)-2-butyl, *tert*-butyl, isobutyl, 1-pentyl, 3-pentyl, 2-methylbutyl, 2,2,2-trifluoroethyl, 6-amidocarbonylhexyl, 4-methyl-2-pentyl, 3-hydroxypropyl, 3-methoxy-2-propyl, 2-methoxyethyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-dimethylaminopropyl, 2-cyanoethyl, 6-hydroxyhexyl, 2-hydroxyethyl, 2-amidinoethyl, 2-guanidinoethyl, 3-guanidinopropyl, 4-guanidinobutyl, 3-hydroxypropyl, 4-hydroxybutyl, 6-cyanoethyl, 2-dimethylaminoethyl, 3-methylbutyl, 2-methylbutyl, (S)-2-methylbutyl, 3-aminopropyl, 2-hexyl, and 4-aminobutyl;

10

15

A is selected from the group consisting of single covalent bond, CH_2 , $NHC(O)$, CH_2CH_2 , $CH_2CH_2CH_2$, and CH_3CHCH_2 ;

20

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, methylamino, cyano, methyl, trifluoromethyl, methoxy, hydroxymethyl, methoxyamino, methylthio, trifluoromethoxy, fluoro, and chloro;

25

R^2 is Z^0-Q ;

Z^0 is selected from the group consisting of a covalent single bond, O, S, NH, and CH_2 ;

Q is selected from the group consisting of 5-amino-3-amidocarbonylphenyl, 5-amino-2-fluorophenyl, 3-amino-5-hydroxymethylphenyl, 5-amino-3-methoxycarbonylphenyl, 3-amidinophenyl,

30

- 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, benzyl, 3-carboxyphenyl, 3-carboxy-5-aminophenyl, 3-carboxy-5-hydroxyphenyl, 3-carboxymethyl-5-aminophenyl, 3-carboxymethyl-5-hydroxyphenyl, 3-carboxymethylphenyl, 3-chlorophenyl, 2-chlorophenyl, 5 2,6-dichlorophenyl, 3-cyanophenyl, 3-dimethylaminophenyl, 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 10 phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;

Y^0 is selected from the group consisting of:

- 1-Q^b-4-Q^s-2-R¹⁶-3-R¹⁷-5-R¹⁸-6-R¹⁹ benzene,
15 2-Q^b-5-Q^s-6-R¹⁷-4-R¹⁸-2-R¹⁹ pyridine,
3-Q^b-6-Q^s-2-R¹⁶-5-R¹⁸-4-R¹⁹ pyridine,
3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ thiophene, and 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ thiophene;

- R¹⁶ and R¹⁹ are independently selected from the group consisting of hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, 20 hydroxymethyl, fluoro, chloro, and cyano;

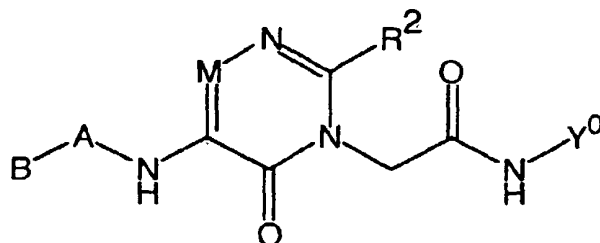
R¹⁶ and R¹⁹ are optionally Q^b with the proviso that no more than one of R¹⁶ and R¹⁹ is Q^b at the same time and that Q^b is Q^{be};

- R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;
25 Q^b is selected from the group consisting of Q^{be} wherein Q^{be} is hydrido and C(NR²⁵)NR²³R²⁴;

R²³, R²⁴, and R²⁵ are independently selected from the group consisting of hydrido and methyl;

Q^s is CH_2 .

20. The compound as recited in Claim 17 having the Formula:



5 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, C2-C8 alkyl, C3-C8 alkenyl, C3-C8 alkynyl, and C2-C8 haloalkyl, wherein each member of group B is optionally substituted at any carbon up to and including 6 atoms from the point of attachment of B to A with one or more of the group

10 consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, 15 haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is $N(R^7)$;

20 R^7 is selected from the group consisting of hydrido and alkyl;

R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

5 R^2 is Z^0 -Q;

Z^0 is a covalent single bond;

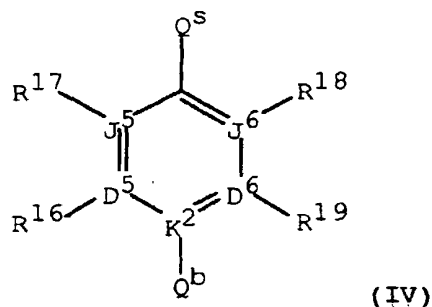
Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is

10 optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

15 R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkylamidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

20 R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, 25 carboxy, carboxyamido, carboxyalkyl, and cyano;

Y^0 is formula (IV):



wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N;

R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, $N(R^{26})C(NR^{25})N(R^{23})(R^{24})$, and $C(NR^{25})NR^{23}R^{24}$;

R^{20} , R^{21} , R^{23} , R^{24} , R^{25} , and R^{26} are independently selected from the group consisting of hydrido and alkyl;

Q^s is CH_2 .

21. The compound as recited in Claim 17 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butenyl, 2-butyne, sec-butyl, *tert*-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 2-methyl-2-butenyl, 3-methylbutyl, 3-methyl-2-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl-4-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R³², R³³, R³⁴, R³⁵, and R³⁶;

20 R³², R³³, R³⁴, R³⁵, and R³⁶ are independently selected from the group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidodisulfonyl, hydroxymethyl, 25 amidocarbonyl, carboxy, cyano, and Q^b;

A is selected from the group consisting of single covalent bond, NH, N(CH₃), CH₂, CH₃CH, and CH₂CH₂;

A is optionally selected from the group consisting of CH₂N(CH₃), CH₂N(CH₂CH₃), CH₂CH₂N(CH₃), and CH₂CH₂N(CH₂CH₃) with the 30 proviso that B is hydrido;

M is selected from the group consisting of N and R¹-C;

R¹ is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, methylamino, cyano, methyl, trifluoromethyl, methoxy, hydroxymethyl, methoxyamino, methylthio, trifluoromethoxy, fluoro, and chloro;

R² is selected from the group consisting of phenyl, 2-thienyl, 2-furyl, 2-pyrrolyl, 2-imidazolyl, 2-thiazolyl, 3-isoxazolyl, 2-pyridyl, and 3-pyridyl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R⁹, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R¹³, a carbon adjacent to R⁹ and two atoms from the carbon at the point of attachment is optionally substituted by R¹⁰, a carbon adjacent to R¹³ and two atoms from the carbon at the point of attachment is optionally substituted by R¹², and any carbon adjacent to both R¹⁰ and R¹² is optionally substituted by R¹¹;

R⁹, R¹¹, and R¹³ are independently selected from the group consisting of hydrido, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, methylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamid sulfonyl, N,N-dimethylamid sulfonyl, hydroxymethyl, 1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, carboxy, and cyano;

R¹⁰ and R¹² are independently selected from the group consisting of hydrido, amidino, amidocarbonyl, N-methylamidocarbonyl, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, carboxy, carboxymethyl, amino, acetamido, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoroacetamido, aminomethyl, N-methylamino, dimethylamino, amidosulfonyl, N-methylamid sulfonyl, N,N-dimethylamid sulfonyl, methoxycarbonyl, fluoro, chloro, bromo, and cyano;

Y⁰ is selected from the group consisting of:

1-Q^b-4-Q^s-2-R¹⁶-3-R¹⁷-5-R¹⁸-6-R¹⁹ benzene,

- 2-Q^b-5-Q^s-6-R¹⁷-4-R¹⁸-2-R¹⁹ pyridine, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ thiophene,
 3-Q^b-6-Q^s-2-R¹⁶-5-R¹⁸-4-R¹⁹ pyridine, 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ thiophene,
 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ furan, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ furan,
 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ pyrrole, 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ pyrrole,
 5 4-Q^b-2-Q^s-5-R¹⁹ thiazole, and 2-Q^b-5-Q^s-4-R¹⁷ thiazole;

- R¹⁶, R¹⁷, R¹⁸, and R¹⁹ are independently selected from the group
 consisting of hydrido, methyl, ethyl, amidino, guanidino, methoxy, hydroxy,
 amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino,
 dimethylamino, methylthio, ethylthio, trifluoromethylthio, methylsulfinyl,
 10 methylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl,
 trifluoromethoxy, fluoro, chloro, amidosulfonyl, N-methylamid sulfonyl,
 hydroxymethyl, carboxy, and cyano.

- Q^b is selected from the group consisting of NR²⁰R²¹,
 C(NR²⁵)NR²³R²⁴, and N(R²⁶)C(NR²⁵)N(R²³)(R²⁴), with the proviso that
 15 said Q^b group is bonded directly to a carbon atom;

R²⁰, R²¹, R²³, R²⁴, R²⁵, and R²⁶ are independently selected from the
 group consisting of hydrido, methyl, and ethyl;

Q^s is CH₂.

- 20 22. The compound as recited in Claim 21 or a pharmaceutically acceptable salt
 thereof, wherein;

- B is selected from the group consisting of hydrido, ethyl, 2-propenyl,
 2-propynyl, propyl, isopropyl, butyl, 2-butyl, (R)-2-butyl, (S)-2-butyl, *tert*-
 butyl, isobutyl, 1-pentyl, 3-pentyl, 2-methylbutyl, 2,2,2-trifluoroethyl, 6-
 25 amidocarbonylhexyl, 4-methyl-2-pentyl, 3-hydroxypropyl, 3-methoxy-2-
 propyl, 2-methoxyethyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-
 dimethylaminopropyl, 2-cyanoethyl, 6-hydroxyhexyl, 2-hydroxyethyl, 2-
 amidinoethyl, 2-guanidinoethyl, 3-guanidinopropyl, 4-guanidinobutyl, 3-

hydroxypropyl, 4-hydroxybutyl, 6-cyanoethyl, 2-dimethylaminoethyl, 3-methylbutyl, 2-methylbutyl, (S)-2-methylbutyl, 3-aminopropyl, 2-hexyl, and 4-aminobutyl;

A is selected from the group consisting of single covalent bond, CH₂,

5 CH₃CH, and CH₂CH₂;

M is selected from the group consisting of N and R¹-C;

R¹ is selected from the group consisting of hydrido, hydroxy, amino, methyl, trifluoromethyl, fluoro, and chloro;

R² is selected from the group consisting of 5-amino-3-
 10 amidocarbonylphenyl, 5-amino-2-fluorophenyl, 3-amino-5-hydroxymethylphenyl, 5-amino-3-methoxycarbonylphenyl, 3-amidinophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, benzyl, 3-carboxyphenyl, 3-carboxy-5-aminophenyl, 3-carboxy-5-hydroxyphenyl, 3-carboxymethyl-5-aminophenyl, 3-carboxymethyl-5-
 15 hydroxyphenyl, 3-carboxymethylphenyl, 3-chlorophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 3-cyanophenyl, 3-dimethylaminophenyl, 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-
 20 methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;

Y⁰ is selected from the group consisting of:

25 1-Q^b-4-Q^s-2-R¹⁶-3-R¹⁷-5-R¹⁸-6-R¹⁹ benzene,
 2-Q^b-5-Q^s-6-R¹⁷-4-R¹⁸-2-R¹⁹ pyridine,
 3-Q^b-6-Q^s-2-R¹⁶-5-R¹⁸-4-R¹⁹ pyridine,
 3-Q^b-5-Q^s-4-R¹⁶-2-R¹⁹ thiophene, and 2-Q^b-5-Q^s-3-R¹⁶-4-R¹⁷ thiophene;

R^{16} and R^{19} are independently selected from the group consisting of hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, hydroxymethyl, fluoro, chloro, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one
 5 of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

R^{17} and R^{18} are independently selected from the group consisting of hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;

Q^b is selected from the group consisting of Q^{be} wherein Q^{be} is hydrido and $C(NR^{25})NR^{23}R^{24}$;

10 R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido and methyl;

Q^s is CH_2 .

23. The compound as recited in Claim 22 or a pharmaceutically acceptable salt
 15 thereof, wherein;

B is selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butyl, (R)-2-butyl, (S)-2-butyl, *tert*-butyl, isobutyl, 1-pentyl, 3-pentyl, 2-methylbutyl, 2,2,2-trifluoroethyl, 6-amidocarbonylhexyl, 4-methyl-2-pentyl, 3-hydroxypropyl, 3-methoxy-2-
 20 propyl, 2-methoxyethyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-dimethylaminopropyl, 2-cyanoethyl, 6-hydroxyhexyl, 2-hydroxyethyl, 2-amidinoethyl, 2-guanidinoethyl, 3-guanidinopropyl, 4-guanidinobutyl, 3-hydroxypropyl, 4-hydroxybutyl, 6-cyanoethyl, 2-dimethylaminoethyl, 3-methylbutyl, 2-methylbutyl, (S)-2-methylbutyl, 3-aminopropyl, 2-hexyl, and
 25 4-aminobutyl;

A is selected from the group consisting of single covalent bond, CH_2 , CH_3CH , and CH_2CH_2 ;

M is selected from the group consisting of N and R^1-C ;

WO 00/69832

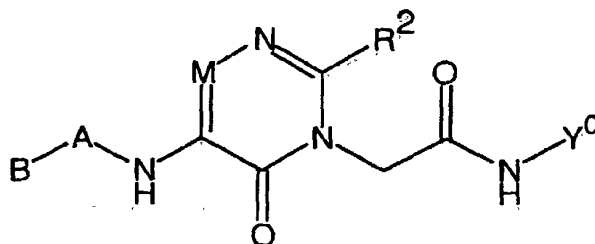
PCT/US00/09806

R^1 is selected from the group consisting of hydrido, fluoro, and chloro;

R^2 is selected from the group consisting of 5-amino-2-fluorophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-methoxycarbonylphenyl, phenyl, and 3-pyridyl;

Y^0 is selected from the group consisting of 5-amidino-2-thienylmethyl, 4-amidinobenzyl, 2-fluoro-4-amidinobenzyl, and 3-fluoro-4-amidinobenzyl.

- 10 24. A compound as recited in Claim 17 where said compound is selected from the group having the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

15 R^2 is 3-aminophenyl, B is 2,2,2-trifluoroethyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is (S)-2-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 5-amino-2-fluorophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

20 R^2 is 2-methyl-3-aminophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is ethyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

25 R^2 is 3-aminophenyl, B is ethyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 2-propenyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CH;

5 R^2 is 3-aminophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 2-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

10 R^2 is 3-aminophenyl, B is (R)-2-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 2-propynyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 3-pentyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

15 R^2 is 3-aminophenyl, B is hydrido, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is ethyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

20 R^2 is 3-aminophenyl, B is 2-methypropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 2-propyl, A is CH_3CH , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is propyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CH;

25 R^2 is 3-aminophenyl, B is 6-amidocarbonylhexyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is tert-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is tert-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 3-hydroxypropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

5 R^2 is 3-aminophenyl, B is 2-methylpropyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

10 R^2 is 3-aminophenyl, B is 3-methoxy-2-propyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 3-methoxy-2-propyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 2-methoxy-2-ethyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

15 R^2 is 3-aminophenyl, B is 2-propyl, A is single bond, Y^0 is 5-amidino-2-thienylmethyl, and M is CH;

R^2 is 3-aminophenyl, B is 2-propyl, A is single bond, Y^0 is 4-amidino-3-fluorobenzyl, and M is CH;

20 R^2 is 3-carboxyphenyl, B is 2-propyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 2-propyl, A is single bond, Y^0 is 4-amidino-3-fluorobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 2,2,2-trifluoroethyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

25 R^2 is 3-aminophenyl, B is (S)-2-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 5-amino-2-fluorophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 2-methyl-3-aminophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is ethyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

5 R^2 is 3-aminophenyl, B is ethyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is N;

R^2 is 3-aminophenyl, B is 2-propenyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

10 R^2 is 3-aminophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is N;

R^2 is 3-aminophenyl, B is isopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is 2-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

15 R^2 is 3-aminophenyl, B is (R)-2-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is 2-propynyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

20 R^2 is 3-aminophenyl, B is 3-pentyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is hydrido, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is ethyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

25 R^2 is 3-aminophenyl, B is 2-methypropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is 2-propyl, A is CH_3CH , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is propyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is N;

R^2 is 3-aminophenyl, B is 6-amidocarbonylhexyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

5 R^2 is 3-aminophenyl, B is tert-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is tert-butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

10 R^2 is 3-aminophenyl, B is 3-hydroxypropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is 2-methylpropyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is N;

R^2 is 3-aminophenyl, B is butyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

15 R^2 is 3-aminophenyl, B is 3-methoxy-2-propyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is 3-methoxy-2-propyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

20 R^2 is 3-aminophenyl, B is 2-methoxy-2-ethyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

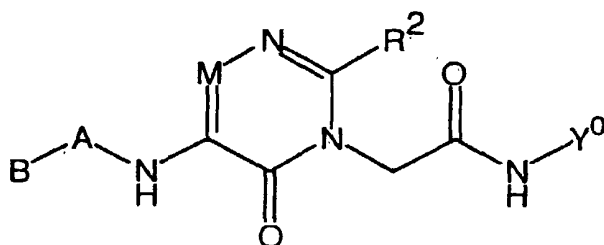
R^2 is 3-aminophenyl, B is 2-propyl, A is single bond, Y^0 is 5-amidino-2-thienylmethyl, and M is N;

R^2 is 3-aminophenyl, B is 2-propyl, A is single bond, Y^0 is 4-amidino-3-fluorobenzyl, and M is N;

25 R^2 is 3-carboxyphenyl, B is 2-propyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is 2-propyl, A is single bond, Y^0 is 4-amidino-3-fluorobenzyl, and M is CH.

25. The compound as recited in Claim 2 having the Formula:



or a pharmaceutically acceptable salt thereof, wherein;

- 5 B is selected from the group consisting of C3-C7 cycloalkyl and C4 saturated heterocyclyl, wherein each ring carbon is optionally substituted with R^{33} , a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbon sand a nitrogen adjacent to
- 10 the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10} , a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12} , a ring carbon three atoms from
- 15 the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11} , a ring carbon three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{33} , and a ring carbon atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34} ;
- 20 R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkylsulfonamido, alkylsulfanyl, alkylsulfonyl,

alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

5 Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$, with the provisos that no more than one of R^{20} and R^{21} is hydroxy at the same time and that no more than one of R^{23} and R^{24} is hydroxy at the same time;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group
10 consisting of hydrido, alkyl, and hydroxy;

Q^s is selected from the group consisting of a single covalent bond, CH_2 , and CH_2CH_2 .

26. The compound as recited in Claim 25 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of cyclopropyl, cyclobutyl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, thiaetan-3-yl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[3.1.0]hexan-6-yl, and cycloheptyl, wherein each ring carbon is optionally substituted with R^{33} , ring
20 carbons and a nitrogen adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10} , and a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted
25 with R^{12} ;

R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, methanesulfonamido, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, carboxymethyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methanesulfonamido, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, fluoro, chloro, bromo, and cyano;

R^{33} and R^{34} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, methoxyamino, ethoxyamino, acetamido, trifluoroacetamido, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, amidocarbonyl, N-methylamidocarbonyl, N,N-dimethylamidocarbonyl, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond, NH, N(CH₃), N(OH), CH₂, CH₃CH, CF₃CH, NHC(O), N(CH₃)C(O), C(O)NH, C(O)N(CH₃), CH₂CH₂, CH₂CH₂CH₂, CH₃CHCH₂, and CF₃CHCH₂;

5 M is selected from the group consisting of N and R¹-C;

R¹ is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, 1-aminoethyl, methylamino, dimethylamino, cyano, methyl, ethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, methoxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 10 methoxyamino, methylthio, ethylthio, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, and bromo;

R² is Z⁰-Q;

Z⁰ is selected from the group consisting of a covalent single bond, O, S, NH, and CH₂;

15 Q is selected from the group consisting of phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, and 1,3,5-triazin-2-yl, wherein a carbon adjacent 20 to the carbon at the point of attachment is optionally substituted by R⁹, the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R¹³, a carbon adjacent to R⁹ and two atoms from the carbon at the point of attachment is optionally substituted by R¹⁰, a carbon adjacent to R¹³ and two atoms from the carbon at the point of attachment is optionally 25 substituted by R¹², and any carbon adjacent to both R¹⁰ and R¹² is optionally substituted by R¹¹;

Y⁰ is selected from the group consisting of:

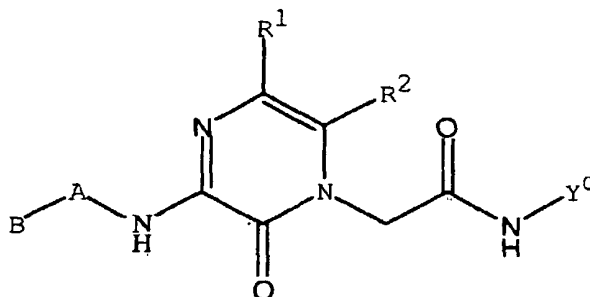
- $1-Q^b-4-Q^s-2-R^{16}-3-R^{17}-5-R^{18}-6-R^{19}$ benzene,
 $2-Q^b-5-Q^s-6-R^{17}-4-R^{18}-2-R^{19}$ pyridine,
 $3-Q^b-6-Q^s-2-R^{16}-5-R^{18}-4-R^{19}$ pyridine, $2-Q^b-4-Q^s-3-R^{16}-6-R^{18}$ pyrazine, $3-Q^b-6-Q^s-2-R^{18}-5-R^{18}-4-R^{19}$ pyridazine,
 5 $2-Q^b-5-Q^s-6-R^{17}-4-R^{18}$ pyrimidine, $5-Q^b-2-Q^s-3-R^{16}-6-R^{19}$ pyrimidine,
 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ thiophene, $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ thiophene,
 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ furan, $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ furan,
 $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ pyrrole, $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ pyrrole,
 $4-Q^b-2-Q^s-5-R^{19}$ imidazole, $2-Q^b-4-Q^s-5-R^{17}$ imidazole,
 10 $3-Q^b-5-Q^s-4-R^{16}$ isoxazole, $5-Q^b-3-Q^s-4-R^{16}$ isoxazole,
 $2-Q^b-5-Q^s-4-R^{16}$ pyrazole, $4-Q^b-2-Q^s-5-R^{19}$ thiazole, and
 $2-Q^b-5-Q^s-4-R^{17}$ thiazole;

- R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, isopropyl, propyl, carboxy, amidino,
 15 guanidino, methoxy, ethoxy, isopropoxy, propoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, N-ethylamino, methylthio, ethylthio, isopropylthio, trifluoromethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, trifluoromethyl,
 20 pentafluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, bromo, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2,2,2-trifluoro-1-hydroxyethyl, and cyano;

- R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of
 25 R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

- hydroxyphenyl, 3-carboxymethylphenyl, 3-chlorophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 3-cyanophenyl, 3-dimethylaminophenyl, 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;
- 5 Y^0 is selected from the group consisting of:
- 10 $1-Q^b-4-Q^s-2-R^{16}-3-R^{17}-5-R^{18}-6-R^{19}$ benzene,
- $2-Q^b-5-Q^s-6-R^{17}-4-R^{18}-2-R^{19}$ pyridine,
- $3-Q^b-6-Q^s-2-R^{16}-5-R^{18}-4-R^{19}$ pyridine,
- $3-Q^b-5-Q^s-4-R^{16}-2-R^{19}$ thiophene, and $2-Q^b-5-Q^s-3-R^{16}-4-R^{17}$ thiophene;
- 15 R^{16} and R^{19} are independently selected from the group consisting of hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, hydroxymethyl, fluoro, chloro, and cyano;
- R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;
- 20 R^{17} and R^{18} are independently selected from the group consisting of hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;
- Q^b is selected from the group consisting of Q^{be} wherein Q^{be} is hydrido and $C(NR^{25})NR^{23}R^{24}$;
- R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of
- 25 hydrido and methyl;
- Q^s is CH_2 .

28. The compound as recited in Claim 25 having the Formula:



or a pharmaceutically acceptable salt thereof, wherein;

- B is selected from the group consisting of C3-C7 cycloalkyl and C4 saturated heterocyclyl, wherein each ring carbon is optionally substituted with R^{33} , a ring carbon other than the ring carbon at the point of attachment of B to A is optionally substituted with oxo provided that no more than one ring carbon is substituted by oxo at the same time, ring carbons and a nitrogen adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10} , a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12} , a ring carbon three atoms from the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11} , a ring carbon three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{33} , and a ring carbon four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34} ;

- R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower

alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

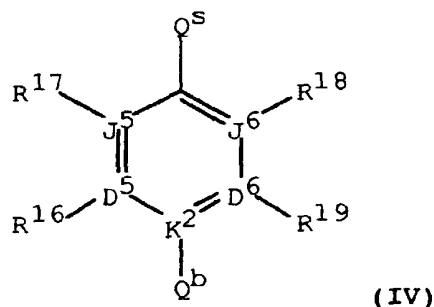
- R^{10} and R^{12} are independently selected from the group consisting of
- 5 hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, carboxy, carboxyalkyl, carboxyamido, and cyano;
- 10 R^{33} and R^{34} are independently selected from the group consisting of hydrido, amidino, guanidino, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboalkoxy, carboxy, carboxamido, and cyano;
- 15 R^{33} is optionally Q^b ;
- A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_r$ wherein r is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is $N(R^7)$;
- R^7 is selected from the group consisting of hydrido and alkyl;
- 20 R^{15} is selected from the group consisting of hydrido, halo, alkyl, and haloalkyl;
- M is selected from the group consisting of N and R^1-C ;
- R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl,
- 25 alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;
- R^2 is Z^0-Q ;
- Z^0 is a covalent single bond;

Q is selected from the group consisting of aryl and heteroaryl wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, hydroxy, amino, amidino, guanidino, lower alkylamino, alkylthio, alkoxy, alkylsulfinyl, alkylsulfonyl, amidosulfonyl, monoalkylamidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, carboxamido, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, amidino, guanidino, alkyl, alkoxy, alkoxyamino, aminoalkyl, hydroxy, amino, lower alkylamino, alkylsulfonamido, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, hydroxyalkyl, aminoalkyl, halo, haloalkyl, carboalkoxy, carboxy, carboxyamido, carboxyalkyl, and cyano;

Y^0 is formula (IV):



wherein D^5 , D^6 , J^5 , and J^6 are independently selected from the group consisting of C, N, O, S and a covalent bond with the provisos that no more than one is a covalent bond, K^2 is C, no more than one of D^5 , D^6 , J^5 , and J^6 is O, no more than one of D^5 , D^6 , J^5 , and J^6 is S, one of D^5 , D^6 , J^5 , and J^6 must be a covalent bond when two of D^5 , D^6 , J^5 , and J^6 are O and S, and no more than four of D^5 , D^6 , J^5 , and J^6 are N;

R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

Q^b is selected from the group consisting of $NR^{20}R^{21}$, Q^{be} wherein Q^{be} is hydrido, and $C(NR^{25})NR^{23}R^{24}$;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido and alkyl;

Q^s is CH_2 .

29. The compound as recited in Claim 28 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-(2R)-bicyclo[2.2.1]-heptyl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, and bicyclo[3.1.0]hexan-6-yl,

wherein each ring carbon is optionally substituted with R^{33} , ring carbons and a nitrogen atom adjacent to the carbon atom at the point of attachment is optionally

substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10} , and a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12} ;

- 5 R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, methylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, hydroxymethyl, 1-hydroxyethyl, amidocarbonyl, 10 N-methylamidocarbonyl, carboxy, and cyano;

- R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, amidocarbonyl, N-methylamidocarbonyl, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, carboxy, carboxymethyl, amino, acetamido, trifluoromethyl, 15 pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoroacetamido, aminomethyl, N-methylamino, dimethylamino, amidosulfonyl, N-methylamidosulfonyl, N,N-dimethylamidosulfonyl, methoxycarbonyl, fluoro, chloro, bromo, and cyano;
- R^{11} are independently selected from the group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, carboxy, 20 amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, amidocarbonyl, cyano, and Q^b ;

A is selected from the group consisting of single covalent bond, NH, N(CH₃), CH₂, CH₃CH, CH₂CH₂, and CH₂CH₂CH₂;

- 25 M is selected from the group consisting of N and R^1 -C;

R^1 is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, methylamino, cyano, methyl, trifluoromethyl, methoxy, hydroxymethyl, methoxyamino, methylthio, trifluoromethoxy, fluoro, and chloro;

Q^b is selected from the group consisting of $NR^{20}R^{21}$ and $C(NR^{25})NR^{23}R^{24}$, with the proviso that said Q^b group is bonded directly to a carbon atom;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, methyl, and ethyl;

Q^s is CH_2 .

30. The compound as recited in Claim 29 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-(2R)-bicyclo[2.2.1]-heptyl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, and azetidin-3-yl;

A is selected from the group consisting of a single covalent bond, CH_2 , $NHC(O)$, CH_2CH_2 and $CH_2CH_2CH_2$;

M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, hydroxy, amino, methyl, trifluoromethyl, fluoro, and chloro;

R^2 is selected from the group consisting of 3-aminophenyl, 2,6-dichlorophenyl, 2-hydroxyphenyl, 5-amino-2-thienyl, and 3-thienyl;

Y^0 is selected from the group consisting of:

1- Q^b -4- Q^s -2- R^{16} -3- R^{17} -5- R^{18} -6- R^{19} benzene,

3- Q^b -5- Q^s -4- R^{16} -2- R^{19} thiophene, and 2- Q^b -5- Q^s -3- R^{16} -4- R^{17} thiophene;

R^{16} and R^{19} are independently selected from the group consisting of hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, hydroxymethyl, fluoro, chloro, and cyano;

R^{16} and R^{19} are optionally Q^b with the proviso that no more than one of R^{16} and R^{19} is Q^b at the same time and that Q^b is Q^{be} ;

R^{17} and R^{18} are independently selected from the group consisting of hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;

Q^b is selected from the group consisting of Q^{be} wherein Q^{be} is hydrido and $C(NR^{25})NR^{23}R^{24}$;

5 R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido and methyl;

Q^s is CH_2 .

10 31. The compound as recited in Claim 30 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-(2R)-bicyclo[2.2.1]-heptyl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, and azetidin-3-yl;

15 A is selected from the group consisting of a single covalent bond, CH_2 , CH_2CH_2 and $CH_2CH_2CH_2$;

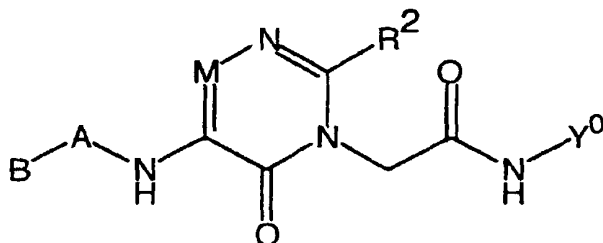
M is selected from the group consisting of N and R^1-C ;

R^1 is selected from the group consisting of hydrido, fluoro, and chloro;

20 R^2 is selected from the group consisting of 3-aminophenyl, 2,6-dichlorophenyl, 2-hydroxyphenyl, phenyl, 5-amino-2-thienyl, and 3-thienyl;

Y^0 is selected from the group consisting of 5-amidino-2-thienylmethyl, 4-amidinobenzyl, 2-fluoro-4-amidinobenzyl, and 3-fluoro-4-amidinobenzyl.

25 32. A compound as recited in Claim 25 where said compound is selected from the group having the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^2 is 3-aminophenyl, B is cyclopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

5 R^2 is 3-aminophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

10 R^2 is 3-aminophenyl, B is cyclopropyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidino-3-fluorobenzyl, and M is CH;

15 R^2 is 3-aminophenyl, B is cyclopentyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 5-amino-2-thienyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

20 R^2 is 3-aminophenyl, B is cyclopropyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 2-(2R)-bicyclo[2.2.1]-heptyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is cyclopentyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CH;

R^2 is 3-aminophenyl, B is 2-(2R)-bicyclo[2.2.1]-heptyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-aminophenyl, B is cyclopentyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is N;

5 R^2 is 3-aminophenyl, B is cyclohexyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 2-hydroxyphenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

10 R^2 is phenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 3-thienyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

R^2 is 2,6-dichlorophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is N;

15 R^2 is 3-aminophenyl, B is cyclopropyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 3-aminophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CF;

20 R^2 is 3-aminophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 3-aminophenyl, B is cyclopropyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CF;

R^2 is 3-aminophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CF;

25 R^2 is 3-aminophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidino-3-fluorobenzyl, and M is CF;

R^2 is 3-aminophenyl, B is cyclopentyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 5-amino-2-thienyl, B is cyclobutyl, A is single bond. Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 3-aminophenyl, B is cyclopropyl, A is CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

5 R^2 is 3-aminophenyl, B is 2-(2R)-bicyclo[2.2.1]-heptyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 3-aminophenyl, B is cyclopentyl, A is single bond, Y^0 is 4-amidino-2-fluorobenzyl, and M is CF;

10 R^2 is 3-aminophenyl, B is cyclohexyl, A is CH_2CH_2 , Y^0 is 4-amidinobenzyl, and M is CF;

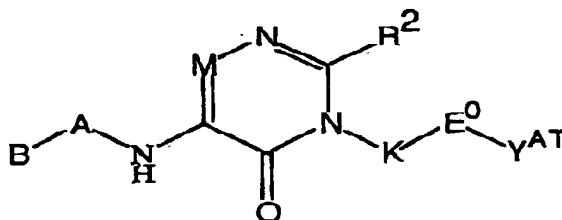
R^2 is 2-hydroxyphenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is phenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CF;

15 R^2 is 3-thienyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CF;

R^2 is 2,6-dichlorophenyl, B is cyclobutyl, A is single bond, Y^0 is 4-amidinobenzyl, and M is CF.

20 33. The compound having the Formula:



or a pharmaceutically acceptable salt thereof, wherein;

B is the Formula:

- substituted with R^{10} , a ring carbon or nitrogen adjacent to the R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12} , a ring carbon three atoms from the point of attachment and adjacent to the R^{10} position is optionally substituted with R^{11} , a ring carbon three atoms from the point of attachment and adjacent to the R^{12} position is optionally substituted with R^{33} , and a ring carbon four atoms from the point of attachment and adjacent to the R^{11} and R^{33} positions is optionally substituted with R^{34} ;
- R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are independently selected from the group consisting of hydrido, acetamido, haloacetamido, alkoxyamino, alkanoyl, haloalkanoyl, amidino, guanidino, alkylendioxy, haloalkylthio, alkoxy, hydroxy, amino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfamido, alkylsulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, carboalkoxy, carboxy, carboxyalkyl, carboxamido, and cyano;
- A is selected from the group consisting of single covalent bond and $(CH(R^{15}))_{pa}-(W^7)_{rr}$ wherein rr is an integer selected from 0 through 1, pa is an integer selected from 0 through 3, and W^7 is selected from the group consisting of O, S, C(O), $(R^7)NC(O)$, $(R^7)NC(S)$, and $N(R^7)$;
- R^7 is selected from the group consisting of hydrido, hydroxy and alkyl;
- R^{15} is selected from the group consisting of hydrido, hydroxy, halo, alkyl, and haloalkyl;
- M is selected from the group consisting of N and R^1-C ;
- R^1 is selected from the group consisting of hydrido, hydroxy, hydroxyamino, amidino, amino, cyano, hydroxyalkyl, alkoxy, alkyl, alkylamino, aminoalkyl, alkylthio, alkoxyamino, haloalkyl, haloalkoxy, and halo;

R^2 is Z^0-Q ;

Z^0 is selected from the group consisting of covalent single bond and $(CR^{41}R^{42})_q$ wherein q is an integer selected from 1 through 2, $(CH(R^{41}))_g-W^0-(CH(R^{42}))_p$ wherein g and p are integers independently selected from 0 through 3 and W^0 is selected from the group consisting of O, S, and $N(R^{41})$, and $(CH(R^{41}))_e-W^{22}-(CH(R^{42}))_h$ wherein e and h are integers independently selected from 0 through 1 and W^{22} is selected from the group consisting of $CR^{41}=CR^{42}$, 1,2-cyclopropyl, 1,2-cyclobutyl, 1,2-cyclohexyl, 1,3-cyclohexyl, 1,2-cyclopentyl, 1,3-cyclopentyl, 2,3-morpholinyl, 2,4-morpholinyl, 2,6-morpholinyl, 3,4-morpholinyl, 3,5-morpholinyl, 1,2-piperazinyl, 1,3-piperazinyl, 2,3-piperazinyl, 2,6-piperazinyl, 1,2-piperidinyl, 1,3-piperidinyl, 2,3-piperidinyl, 2,4-piperidinyl, 2,6-piperidinyl, 3,4-piperidinyl, 1,2-pyrrolidinyl, 1,3-pyrrolidinyl, 2,3-pyrrolidinyl, 2,4-pyrrolidinyl, 2,5-pyrrolidinyl, 3,4-pyrrolidinyl, 2,3-tetrahydrofuranyl, 2,4-tetrahydrofuranyl, 2,5-tetrahydrofuranyl, and 3,4-tetrahydrofuranyl, with the proviso that Z^0 is directly bonded to the pyrazinone ring;

R^{41} and R^{42} are independently selected from the group consisting of hydrido, hydroxy, and amino;

Q is selected from the group consisting of hydrido with the proviso that Z^0 is other than a covalent single bond, aryl and heteroaryl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally

substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

K is CHR^{4a} wherein R^{4a} is selected from the group consisting of hydrido, hydroxyalkyl, alkyl, alkoxyalkyl, alkylthioalkyl, and haloalkyl;

5 E^0 is selected from the group consisting of a covalent single bond, $C(O)N(H)$, $(H)NC(O)$, $(R^7)NS(O)_2$, and $S(O)_2N(R^7)$;

Y^{AT} is Q^b-Q^s ;

Q^s is $(CR^{37}R^{38})_b$ wherein b is an integer selected from 1 through 4,

R^{37} is selected from the group consisting of hydrido, alkyl, and haloalkyl, and

10 R^{38} is selected from the group consisting of hydrido, alkyl, haloalkyl, aroyl, and heteroaroyl with the provisos that there is at least one aroyl or heteroaroyl substituent, that no more than one aroyl or heteroaroyl is bonded to

$(CR^{37}R^{38})_b$ at the same time, that said aroyl and said heteroaroyl are

optionally substituted at from one through three of the ring carbons with a

15 substituent selected from the group consisting of R^{16} , R^{17} , R^{18} , and R^{19} ,

that said aroyl and said heteroaroyl are bonded to the $CR^{37}R^{38}$ that is directly

bonded to E^0 , that is no more than one alkyl or one haloalkyl is bonded to a

$CR^{37}R^{38}$ at the same time, and that said alkyl and haloalkyl are bonded to a

carbon other than the one bonding the aroyl or heteroaroyl;

20 R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, amidino, guanidino, carboxy, haloalkylthio, alkoxy, hydroxy, amino, alkoxyamino, lower alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyl, haloalkanoyl, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, and cyano;

R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} are independently selected from the group consisting of hydrido, amidino, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, amidocarbonyl, carboxy, cyano, and Q^b ;

B is optionally selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butenyl, 2-butylnyl, sec-butyl, *tert*-butyl, isobutyl, 2-methylpropenyl, 1-pentyl, 2-pentenyl, 3-pentenyl, 2-pentynyl, 3-pentynyl, 2-pentyl, 3-pentyl, 2-methylbutyl, 2-methyl-2-butenyl, 3-methylbutyl, 3-methyl-2-butenyl, 1-hexyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 2-hexyl, 1-methyl-2-pentenyl, 1-methyl-3-pentenyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 3-hexyl, 1-ethyl-2-butenyl, 1-heptyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 5-heptynyl, 2-heptyl, 1-methyl-2-hexenyl, 1-methyl-3-hexenyl, 1-methyl-4-hexenyl, 1-methyl-2-hexynyl, 1-methyl-3-hexynyl, 1-methyl-4-hexynyl, 3-heptyl, 1-ethyl-2-pentenyl, 1-ethyl-3-pentenyl, 1-ethyl-2-pentynyl, 1-ethyl-3-pentynyl, 2,2,2-trifluoroethyl, 2,2-difluoropropyl, 4-trifluoromethyl-5,5,5-trifluoropentyl, 4-trifluoromethylpentyl, 5,5,6,6,6-pentafluorohexyl, and 3,3,3-trifluoropropyl, wherein each member of group B is optionally substituted at any carbon up to and including 5 atoms from the point of attachment of B to A with one or more of the group consisting of R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} ;

B is optionally selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-(2R)-bicyclo[2.2.1]-heptyl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, and bicyclo[3.1.0]hexan-6-yl, wherein each ring carbon is optionally substituted with R^{33} , ring carbons and anitrogen adjacent to the carbon atom at the point of attachment is optionally substituted with R^9 or R^{13} , a ring carbon or nitrogen adjacent to the R^9 position and two atoms from the point of attachment is optionally substituted with R^{10} , and a ring carbon or nitrogen adjacent to the

R^{13} position and two atoms from the point of attachment is optionally substituted with R^{12} ;

R^9 , R^{11} , and R^{13} are independently selected from the group consisting of hydrido, methyl, ethyl, methoxy, ethoxy, hydroxy, amino, N-methylamino, N,N-dimethylamino, methylthio, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro, bromo, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, hydroxymethyl, 1-hydroxyethyl, amidocarbonyl, N-methylamidocarbonyl, carboxy, and cyano;

R^{10} and R^{12} are independently selected from the group consisting of hydrido, amidino, amidocarbonyl, N-methylamidocarbonyl, guanidino, methyl, ethyl, methoxy, ethoxy, hydroxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, carboxy, carboxymethyl, amino, acetamido, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoroacetamido, aminomethyl, N-methylamino, dimethylamino, amidosulfonyl, N-methylamidodisulfonyl, N,N-dimethylamidodisulfonyl, methoxycarbonyl, fluoro, chloro, bromo, and cyano;

A is selected from the group consisting of single covalent bond, NH, N(CH₃), CH₂, CH₃CH, CH₂CH₂, and CH₂CH₂CH₂;

M is selected from the group consisting of N and R^1 -C;

R^1 is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, 1-aminoethyl, methylamino, dimethylamino, cyano, methyl, ethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, methoxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxyamino, methylthio, ethylthio, trifluoromethoxy, 1,1,2,2-tetrafluoroethoxy, fluoro, chloro, and bromo;

R^2 is selected from the group consisting of phenyl, 2-thienyl, 2-furyl, 2-pyrrolyl, 2-imidazolyl, 2-thiazolyl, 3-isoxazolyl, 2-pyridyl, and 3-pyridyl, wherein a carbon adjacent to the carbon at the point of attachment is optionally substituted by R^9 , the other carbon adjacent to the carbon at the point of attachment is optionally substituted by R^{13} , a carbon adjacent to R^9 and two atoms from the carbon at the point of attachment is optionally substituted by

R^{10} , a carbon adjacent to R^{13} and two atoms from the carbon at the point of attachment is optionally substituted by R^{12} , and any carbon adjacent to both R^{10} and R^{12} is optionally substituted by R^{11} ;

Y^{AT} is Q^b-Q^s ;

5 Q^s is selected from the group consisting of:

$C[R^{37}(\text{benzoyl})](CR^{37}R^{38})_b$,

$C[R^{37}(2\text{-pyridylcarbonyl})](CR^{37}R^{38})_b$,

$C[R^{37}(3\text{-pyridylcarbonyl})](CR^{37}R^{38})_b$,

$C[R^{37}(4\text{-pyridylcarbonyl})](CR^{37}R^{38})_b$,

10 $C[R^{37}(2\text{-thienylcarbonyl})](CR^{37}R^{38})_b$,

$C[R^{37}(3\text{-thienylcarbonyl})](CR^{37}R^{38})_b$,

$C[R^{37}(2\text{-thiazolylcarbonyl})](CR^{37}R^{38})_b$,

$C[R^{37}(4\text{-thiazolylcarbonyl})](CR^{37}R^{38})_b$, and

$C[R^{37}(5\text{-thiazolylcarbonyl})](CR^{37}R^{38})_b$, wherein b is an integer selected

15 from 1 through 3, R^{37} and R^{38} are independently selected from the group consisting of hydrido, alkyl, and haloalkyl, with the provisos that said aroyl and said heteroaroyl are optionally substituted at from one through three of the ring carbons with a substituent selected from the group consisting of R^{16} , R^{17} , R^{18} , and R^{19} with the proviso that R^{17} and R^{18} are optionally

20 substituted at a carbon selected from other than the meta and para carbons relative to the carbonyl of the benzoyl substituent and the heteroaroyl substituent, that said benzoyl and said heteroaroyl are bonded to the carbon directly bonded to amide nitrogen of the 1-(amidocarbonylmethylene) group,

and that is no more than one alkyl or one haloalkyl is bonded to a $CR^{37}R^{38}$ at the same time;

R^{16} , R^{17} , R^{18} , and R^{19} are independently selected from the group consisting of hydrido, methyl, ethyl, amidino, guanidino, methoxy, hydroxy, amino, aminomethyl, 1-aminoethyl, 2-aminoethyl, N-methylamino, dimethylamino, methylthio, ethylthio, trifluoromethylthio, methylsulfinyl, methylsulfonyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, trifluoromethoxy, fluoro, chloro, amidosulfonyl, N-methylamidosulfonyl, hydroxymethyl, carboxy, and cyano;

Q^b is selected from the group consisting of $NR^{20}R^{21}$ and $C(NR^{25})NR^{23}R^{24}$, with the proviso that said Q^b group is bonded directly to a carbon atom;

R^{20} , R^{21} , R^{23} , R^{24} , and R^{25} are independently selected from the group consisting of hydrido, methyl, and ethyl.

35. The compound as recited in Claim 34 or a pharmaceutically acceptable salt thereof, wherein;

B is selected from the group consisting of 2-aminophenyl, 3-aminophenyl, 3-amidinophenyl, 4-amidinophenyl, 3-carboxyphenyl, 3-carboxy-5-hydroxyphenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-methoxyaminophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, and 3-trifluoromethylphenyl;

B is optionally selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butyl, (R)-2-butyl, (S)-2-butyl, *tert*-butyl, isobutyl, 1-pentyl, 3-pentyl, 2-methylbutyl, 2,2,2-trifluoroethyl, 6-amidocarbonylhexyl, 4-methyl-2-pentyl, 3-hydroxypropyl, 3-methoxy-2-propyl, 2-methoxyethyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-dimethylaminopropyl, 2-cyanoethyl, 6-hydroxyhexyl, 2-hydroxyethyl, 2-amidinoethyl, 2-guanidinoethyl, 3-guanidinopropyl, 4-guanidinobutyl, 3-hydroxypropyl, 4-hydroxybutyl, 6-cyanohexyl, 2-dimethylaminoethyl, 3-

methylbutyl, 2-methylbutyl, (S)-2-methylbutyl, 3-aminopropyl, 2-hexyl, and 4-aminobutyl;

B is optionally selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-(2R)-bicyclo[2.2.1]-heptyl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, and azetidin-3-yl;

A is selected from the group consisting of single covalent bond, CH₂, CH₃CH, CH₂CH₂, and CH₂CH₂CH₂;

M is selected from the group consisting of N and R¹-C;

R¹ is selected from the group consisting of hydrido, hydroxy, amino, amidino, hydroxyamino, aminomethyl, methylamino, cyano, methyl, trifluoromethyl, methoxy, hydroxymethyl, methoxyamino, methylthio, trifluoromethoxy, fluoro, and chloro;

R² is selected from the group consisting of 5-amino-3-amidocarbonylphenyl, 5-amino-2-fluorophenyl, 3-amino-5-hydroxymethylphenyl, 5-amino-3-methoxycarbonylphenyl, 3-amidinophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-aminophenyl, benzyl, 3-carboxyphenyl, 3-carboxy-5-aminophenyl, 3-carboxy-5-hydroxyphenyl, 3-carboxymethyl-5-aminophenyl, 3-carboxymethyl-5-hydroxyphenyl, 3-carboxymethylphenyl, 3-chlorophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 3-cyanophenyl, 3-dimethylaminophenyl, 2-fluorophenyl, 3-fluorophenyl, 2,5-difluorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methoxyaminophenyl, 3-methoxycarbonylphenyl, 2-methylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, phenyl, 3-trifluoroacetamidophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 5-amino-2-thienyl, 5-amino-3-thienyl, 3-bromo-2-thienyl, 3-pyridyl, 4-pyridyl, 2-thienyl, and 3-thienyl;

Y^{AT} is Q^b-Q^s;

Q^s is selected from the group consisting of:

[CH(benzoyl)](CH₂)_b, [CH(2-pyridylcarbonyl)](CH₂)_b,

[CH(3-pyridylcarbonyl)](CH₂)_b, [CH(4-pyridylcarbonyl)](CH₂)_b,

[CH(2-thienylcarbonyl)](CH₂)_b, [CH(3-thienylcarbonyl)](CH₂)_b,

[CH(2-thiazolylcarbonyl)](CH₂)_b, [CH(4-thiazolylcarbonyl)](CH₂)_b,

and [CH(5-thiazolylcarbonyl)](CH₂)_b, wherein b is an integer selected from 1

5 through 3, with the provisos that said aroyl and said heteroaroyl are optionally substituted at from one through three of the ring carbons with a substituent selected from the group consisting of R¹⁶, R¹⁷, R¹⁸, and R¹⁹ with the

proviso that R¹⁷ and R¹⁸ are optionally substituted at a carbon selected from other than the meta and para carbons relative to the carbonyl of the benzoyl substituent and the heteroaroyl substituent, and that said benzoyl and said heteroaroyl substituent are bonded to the carbon directly bonded to amide nitrogen of the 1-(amidocarbonylmethylene) group;

10 R¹⁶ and R¹⁹ are independently selected from the group consisting of hydrido, amidino, amino, aminomethyl, methoxy, methylamino, hydroxy, hydroxymethyl, fluoro, chloro, and cyano;

15 R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrido, fluoro, chloro, hydroxy, hydroxymethyl, amino, carboxy, and cyano;

Q^b is C(NR²⁵)NR²³R²⁴;

20 R²³, R²⁴, and R²⁵ are independently selected from the group consisting of hydrido and methyl.

36. The compound as recited in Claim 35 or a pharmaceutically acceptable salt thereof, wherein;

25 B is selected from the group consisting of 3-aminophenyl, 3-amidinophenyl, 4-amidinophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 2-fluorophenyl, 4-methylphenyl, and phenyl;

B is optionally selected from the group consisting of hydrido, ethyl, 2-propenyl, 2-propynyl, propyl, isopropyl, butyl, 2-butyl, (R)-2-butyl, (S)-2-butyl, *tert*-butyl, isobutyl, 1-pentyl, 3-pentyl, 2-methylbutyl, 2,2,2-

trifluoroethyl, 6-amidocarbonylhexyl, 4-methyl-2-pentyl, 3-hydroxypropyl, 3-methoxy-2-propyl, 2-methoxyethyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-dimethylaminopropyl, 2-cyanoethyl, 6-hydroxyhexyl, 2-hydroxyethyl, 2-amidinoethyl, 2-guanidinoethyl, 3-guanidinopropyl, 4-guanidinobutyl, 3-hydroxypropyl, 4-hydroxybutyl, 6-cyanoethyl, 2-dimethylaminoethyl, 3-methylbutyl, 2-methylbutyl, (S)-2-methylbutyl, 3-aminopropyl, 2-hexyl, and 4-aminobutyl;

B is optionally selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-(2R)-bicyclo[2.2.1]-heptyl, oxetan-3-yl, azetidin-1-yl, azetidin-2-yl, and azetidin-3-yl;

A is selected from the group consisting of a single covalent bond, CH_2 , CH_2CH_2 and $\text{CH}_2\text{CH}_2\text{CH}_2$;

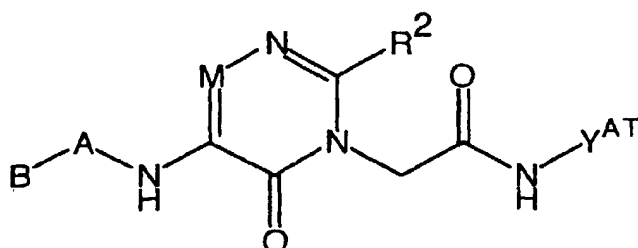
M is selected from the group consisting of N and $\text{R}^1\text{-C}$;

R^1 is selected from the group consisting of hydrido, hydroxy, amino, methyl, trifluoromethyl, fluoro, and chloro;

R^2 is selected from the group consisting of 3-aminophenyl, benzyl, 2,6-dichlorophenyl, 5-amino-2-thienyl, 5-amino-2-fluorophenyl, 3-amino-2-methylphenyl, 5-amino-2-methylthiophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-chlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-methanesulfonylaminophenyl, 3-methoxycarbonylphenyl, 3-dimethylaminophenyl, 3-methylaminophenyl, 2-methylphenyl, 3-methylphenyl, phenyl, 3-pyridyl, 3-trifluoroacetamidophenyl, 3-bromo-2-thienyl, 2-thienyl, and 3-thienyl;

Y^{AT} is selected from the group consisting of 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, 5-guanidino-1-oxo-1-(4-thiazolyl)-2-pentyl, 5-guanidino-1-oxo-1-(5-thiazolyl)-2-pentyl, 5-guanidino-1-oxo-1-(4-amino-2-thiazolyl)-2-pentyl, and 5-guanidino-1-oxo-1-phenyl-2-pentyl.

37. A compound as recited in Claim 33 where said compound is selected from the group having the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^2 is 3-aminophenyl, B is phenyl, A is CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CH;

5 R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CH;

R^2 is benzyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CH;

10 R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CH;

R^2 is benzyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CH;

R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CH;

15 R^2 is 3-aminophenyl, B is phenyl, A is CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CF;

R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CF;

20 R^2 is benzyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CF;

R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CF;

R^2 is benzyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CF;

R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CF;

5 R^2 is 3-aminophenyl, B is phenyl, A is CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CCl;

R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CCl;

10 R^2 is benzyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CCl;

R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CCl;

R^2 is benzyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CCl;

15 R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is CCl;

R^2 is 3-aminophenyl, B is phenyl, A is CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is N;

20 R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is N;

R^2 is benzyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is N;

R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is N;

25 R^2 is benzyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is N;

R^2 is phenyl, B is phenyl, A is CH_2CH_2 , Y^{AT} is 5-guanidino-1-oxo-1-(2-thiazolyl)-2-pentyl, and M is N.

- 5 38. A composition for inhibiting thrombotic conditions in blood comprising a compound of any one of Claims 8, 16, 24, 32, and 37 and a pharmaceutically acceptable carrier.
- 10 39. A composition for inhibiting thrombotic conditions in blood comprising a compound of any one of Claims 1 through 7, Claims 9 through 15, Claims 17 through 23, Claims 25 through 31, and Claims 33 through 36 and a pharmaceutically acceptable carrier.
- 15 40. A method for inhibiting thrombotic conditions in blood comprising adding to blood a therapeutically effective amount of a composition of any one of Claims 38 and 39.
- 20 41. A method for inhibiting formation of blood platelet aggregates in blood comprising adding to blood a therapeutically effective amount of a composition of any one of Claims 38 and 39.
- 25 42. A method for inhibiting thrombus formation in blood comprising adding to blood a therapeutically effective amount of a composition of any one of Claims 38 and 39.
- 30 43. A method for treating or preventing venous thromboembolism and pulmonary embolism in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 38 and 39.
44. A method for treating or preventing deep vein thrombosis in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 38 and 39.

45. A method for treating or preventing cardiogenic thromboembolism in a mammal comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 38 and 39.
- 5 46. A method for treating or preventing thromboembolic stroke in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 38 and 39.
- 10 47. A method for treating or preventing thrombosis associated with cancer and cancer chemotherapy in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 38 and 39.
- 15 48. A method for treating or preventing unstable angina in humans and other mammals comprising administering to the mammal a therapeutically effective amount of a composition of any one of Claims 38 and 39.
- 20 49. A method for inhibiting thrombus formation in blood comprising adding to blood a therapeutically effective amount of a compound of any one of Claims 1 through 37 with a therapeutically effective amount of fibrinogen receptor antagonist.
- 25 50. The use of a compound of any one of Claims 1 through 37, or a pharmaceutically acceptable salt thereof, in the manufacture of medicament for inhibiting thrombus formation, treating thrombus formation, or preventing thrombus formation in a mammal.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 239/46, 253/06, 401/04, 417/12, A61K 31/505, A61P 9/00		A1	(11) International Publication Number: WO 00/69832
			(43) International Publication Date: 23 November 2000 (23.11.00)
(21) International Application Number: PCT/US00/09806		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 17 May 2000 (17.05.00)		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(30) Priority Data: 60/134,794 19 May 1999 (19.05.99) US			
(71) Applicant (for all designated States except US): MONSANTO COMPANY [US/US]; P.O. Box 5110, Chicago, IL 60680-5110 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): SOUTH, Michael, S. [US/US]; 11671 Chieftain Drive, St. Louis, MO 63146 (US). HAMME, Ashton, T., II [US/US]; 1501 B Oak Forest Parkway Ct., St. Louis, MO 63146 (US). NEUMANN, William [US/US]; 212 West Monroe, St. Louis, MO 63122 (US). JONES, Darin, E. [US/US]; 408 Johanna Place, Ballwin, MO 63021 (US). RUEPPEL, Melvin, L. [US/US]; 1904 Grassy Ridge Road, St. Louis, MO 63122 (US).			
(74) Agents: WILLIAMS, Roger, A. et al.; Corporate Patent Dept., Monsanto Company, P.O. Box 5110, Chicago, IL 60680-5110 (US).			
(54) Title: SUBSTITUTED POLYCYCLIC ARYL AND HETEROARYL PYRIMIDINONES USEFUL AS ANTICOAGULANTS			
(57) Abstract The invention relates to substituted polycyclic aryl and heteroaryl pyrimidinone compounds useful as inhibitors of serine proteases of the coagulation cascade and compounds, compositions and methods for anticoagulant therapy for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular diseases.			

Attorney's Docket No. 3203/1A(PHA 4159.26)

DECLARATION AND POWER OF ATTORNEY

REGULAR OR DESIGN APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**SUBSTITUTED POLYCYCLIC ARYL AND HETEROARYL
PYRIMIDINONES USEFUL AS ANTICOAGULANTS**

the specification of which:

(check one)

☐ is attached hereto

☒ was filed on November 13, 2001 as Application Serial No. 10/009,447, and was amended on _____.

☒ was described and claimed in PCT International Application No. PCT/US00/09806, filed on 17 May 2000 and as amended under PCT Article 19 on _____, if any.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56.

PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a) - (d) or §365(b) of any foreign application for patent or inventor's certificate, or §365(a) of any PCT application which designates at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed

<u>PCT/US00/09806</u>	<u>WIPO</u>	<u>17 May 2000</u>
(Number)	(Country)	(Day/Month/Year Filed)
<u> </u>	<u> </u>	<u> </u>
(Number)	(Country)	(Day/Month/Year Filed)

Priority Not Claimed

ANY FOREIGN APPLICATION(S), ON THE SAME SUBJECT MATTER WHICH HAS A FILING DATE EARLIER THAN THE EARLIEST APPLICATION FROM WHICH PRIORITY IS CLAIMED

<u> </u>	<u> </u>	<u> </u>
(Number)	(Country)	(Day/Month/Year Filed)

CLAIM FOR BENEFIT OF PROVISIONAL APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

<u>60/134,794</u>	<u>05-19-1999</u>
(Application Number)	(Filing Date)
<u> </u>	<u> </u>
(Application Number)	(Filing Date)

Send Correspondence To:

Direct Telephone Calls To:

Customer Number: 000321

Kathryn J. Doty
(314) 231-5400

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.


Full name of sole or first inventor Michael S. South
Inventor's signature Michael S. South Date 1-31-02
Residence St. Louis, Missouri MO Citizenship US
Post Office address 11671 Chieftain Drive, St. Louis, MO 63146


Full name of second joint inventor Ashton T. Hamme, II

Second inventor's signature _____ Date _____

Residence St. Louis, Missouri MO Citizenship US

Post Office address 1501 B Oak Forest Parkway Ct., St. Louis, MO
63146

Full name of third joint inventor William L. Neumann
Second inventor's signature  Date 2-01-02
Residence St. Louis, Missouri MO Citizenship US
Post Office address 212 West Monroe, St. Louis, MO 63122

Full name of fourth joint inventor Darin E. Jones
 Second inventor's signature  Date 2-25-02
 Residence Ballwin, Missouri MO Citizenship US
 Post Office address 408 Johanna Place, Ballwin, MO 63021

Send Correspondence To:

Direct Telephone Calls To:

Customer Number: 000321

Kathryn J. Doty
(314) 231-5400

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Michael S. SouthInventor's signature Michael S. South Date 1-31-02Residence St. Louis, Missouri Citizenship USPost Office address 11671 Chieftain Drive, St. Louis, MO 63146Full name of second joint inventor Ashton T. Hamme, IISecond inventor's signature Ashton Hamme Date 3/27/02Residence St. Louis, Missouri Citizenship USPost Office address 1501 B Oak Forest Parkway Ct., St. Louis, MO 63146Full name of third joint inventor William L. NeumannSecond inventor's signature William L. Neumann Date 2-01-02Residence St. Louis, Missouri Citizenship USPost Office address 212 West Monroe, St. Louis, MO 63122Full name of fourth joint inventor Darin E. JonesSecond inventor's signature Darin E. Jones Date 2-25-02Residence Ballwin, Missouri Citizenship USPost Office address 408 Johanna Place, Ballwin, MO 63021

Full name of fifth joint inventor Melvin L. Rueppel

Second inventor's signature *M. Rueppel* Date 1/23/02

Residence St. Louis, Missouri Citizenship US

Post Office address 1904 Grassy Ridge Road, St. Louis, MO 63122

CLAIM FOR BENEFIT OF EARLIER U.S. APPLICATION(S)
UNDER 35 U.S.C. 120

(complete this part only if this is a divisional,
continuation or CIP application)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Serial No.)	(Filing Date)	(Status)
(Serial No.)	(Filing Date)	(Status)

POWER OF ATTORNEY

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Irving Powers (15,700), Donald G. Leavitt (17,626), John K. Roedel, Jr. (25,914), Michael E. Godar (28,416), Edward J. Hejlek (31,525), William E. Lahey (26,757), Richard G. Heywood (18,224), Frank R. Agovino (27,416), Kurt F. James (33,716), G. Harley Blosser (33,650), Paul I. J. Fleischut (35,513), Vincent M. Keil (36,838), Robert M. Evans, Jr. (36,794), Robert M. Bain (36,736), Kathleen M. Petrillo (35,076), David E. Crawford, Jr. (38,118), Richard L. Bridge (40,529), Christopher M. Goff (41,785), Derick E. Allen (43,468), Michael G. Munsell (43,820), Anthony R. Kinney (44,834), Brian P. Klein (44,837), Sarah J. Chickos (46,157), Donald W. Tuegel (45,424), Steven M. Ritchey (46,321), Michael J. Thomas (39,857), Kathryn J. Doty (40,593), Laura R. Polcyn (47,000), James J. Barta, Jr. (47,409), John M. Bodenhausen (47,432), James E. Davis (47,516), Richard A. Schuth (47,929), Debra D. Nye (48,260), Jennifer E. Hoekel (P-48,330), Timothy B. McBride (47,781), George R. Beck (21,180), Dennis A. Bennett (34,547), Jon A. Beusen (30,610), Gary M. Bond (29,283), Grace L. Bonner (32,963), James C. Forbes (39,457), J. Timothy Keane (27,808), Cynthia S. Kovacevic (35,578), Thomas P. McBride (32,706), Michael J. Roth (29,342), Richard H. Shear (26,583), Brian K. Stierwalt (33,213), and Scott A. Williams (39,876).

47